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Genetic manipulation of cyclic nucleotide signaling during hippocampal neuroplasticity and memory formation

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ABSTRACT

Decades of research have underscored the importance of cyclic nucleotide signaling in memory formation and synaptic plasticity. In recent years, several new genetic techniques have expanded the neuroscience toolbox, allowing researchers to measure and modulate cyclic nucleotide gradients with high spatiotemporal resolution. Here, we will provide an overview of studies using genetic approaches to interrogate the role cyclic nucleotide signaling plays in hippocampus-dependent memory processes and synaptic plasticity. Particular attention is given to genetic techniques that measure real-time changes in cyclic nucleotide levels as well as newly-developed genetic strategies to transiently manipulate cyclic nucleotide signaling in a subcellular compartment-specific manner with high temporal resolution.

1. Introduction

1.1. Memory types, systems and processes

Memory is the process of acquiring, retaining and reconstructing information over time (Kandel et al., 2014; McGaugh, 2000). Much has been learned over the last two centuries regarding the fact that there are different types of memory, each with distinguishable anatomical circuits and molecular mechanisms. A general distinction can be made between *short-term memory*, *intermediate* memory, *long-term memory*, and *working memory* (Bear et al., 2007). Working memory is the information we can readily work with (Baddeley, 1992; Goldman-Rakic, 1995). Short-term memory is information that is held by the brain on a temporary basis, lasting in the order of seconds to hours, and relies on changes in intracellular signaling cascades (Manohar et al., 2017). Intermediate memory encompasses the transition from short-term to long-term memory that occurs within the first several hours following the acquisition of new information (Sutton and Carew, 2002). Intermediate memory relies not only on changes in intracellular signaling but also de novo protein synthesis. Long-term memory, on the other hand, is the information that is stored by the brain over a much longer period, easily lasting days to years, and relies on changes in intracellular signaling, de novo transcription, and de novo translation (Jarome and Helmstetter, 2014). In the current review, we will focus on long-term memory.

Long-term memory is divided into *declarative* versus *non-declarative* memory systems (a.k.a. *explicit* versus *implicit* memory systems) (Kandel et al., 2014). Declarative memory mainly requires the hippocampus and medial temporal lobe for its proper functioning; whereas, non-declarative memory recruits brain areas such as the striatum and cerebellum. The declarative memory system includes *episodic* memories of autobiographical life experiences and *semantic* memories of facts. The non-declarative memory system encompasses *procedural* memories of skills, *associative* memories of conditioning, *non-associative memories of* habituation and adaptation), and *priming*. This review primarily focuses on hippocampus-dependent declarative memory processes.

Memory formation involves *acquisition*, *consolidation* and *retrieval* (Fig. 1) (Abel and Lattal, 2001). In the case of acquiring hippocampus-dependent memories, attention is required to transfer sensory information to short-term memory or working memory (Abel and Lattal, 2001). For these short-term memories to be stored long term, they must undergo consolidation. It is suggested there are three stages of consolidation, early consolidation resulting in intermediate memory, late consolidation resulting in recent long-term memory, and systems consolidation resulting in remote long-term memory (Frankland and Bontempi, 2005; Kesner and Hopkins, 2006; McGaugh, 2000). As noted above, short-term hippocampus-dependent memory is encoded by transient changes in neuronal transmission within the hippocampus that require neither gene expression nor protein synthesis. In contrast, intermediate memory and recent long-term hippocampus-dependent

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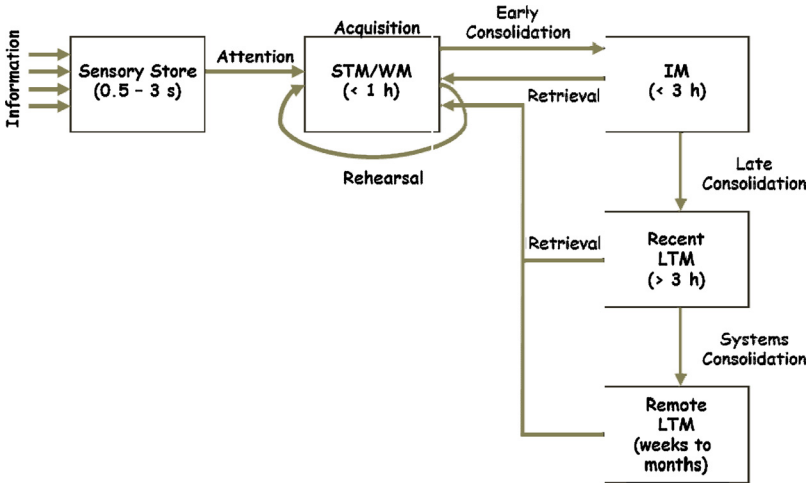

Fig. 1. Schematic classification of the hippocampal memory system including its memory types (short-term memory, long-term memory and working memory) and processes (acquisition, consolidation and retrieval) during synaptic consolidation. STM = short-term memory; WM = working memory; IM = intermediate memory; LTM = long-term memory (figure partially based on Reneerkens et al., 2009).

memory storage are maintained by stable neuronal changes that are dependent on protein synthesis within the hippocampus (*e.g.*, Heckman et al., 2018; Izquierdo et al., 2002). These changes in synaptic strength within the hippocampus are referred to as *cellular consolidation* or *synaptic consolidation*. As these hippocampus-dependent recent long-term memories (engrams) mature over the course of many weeks, they become less dependent on the hippocampus and more dependent on other brain regions like the cortex, with the resultant memories referred to as remote long-term memories (Frankland and Bontempi, 2005). The Standard Theory of Systems Consolidation suggest the hippocampus "replays" the memory to other brain regions in order to promote waves of cellular/synaptic consolidation therein, with the hippocampal trace ultimately erased or silenced (Frankland and Bontempi, 2005; Kitamura et al., 2017; Klinzing et al., 2019). That said, recent findings may challenge this theory (Pilarzyk et al., 2019). Memory retrieval is the process of accessing this stored information and bringing it back into short-term or working memory. During retrieval, information can be updated/altered and subsequently reconsolidated (Abel and Lattal, 2001; Phelps and Hofmann, 2019). In this review, we will focus on cellular/synaptic consolidation of episodic memories in the hippocampus.

1.2. The hippocampus

The hippocampus is regarded as a central structure for episodic learning and memory processes. It is a bilateral structure located in the medial temporal lobe, adjacent to the lateral ventricle. The hippocampus is surrounded by the entorhinal, perirhinal and parahippocampal cortices as well as the amygdala, which provide the hippocampus with sensory information processed by higher cortical association areas. The hippocampus consists of multiple subfields, namely the dentate gyrus, cornu ammonis 1 (CA1), CA2, CA3 and CA4, with CA1 further subdivided into proximal versus distal and superficial versus deep layers. Across species, the hippocampus is not a singular brain structure, but rather is specialized along its axis (dorsal-ventral in rodents, posterior-anterior in primates) in terms of gene expression gradients, inputs/outputs, and brain function (Fanselow and Dong, 2010; Strange et al., 2014). In rodents, both the dorsal and ventral part play a role in various types of learning and memory. The dorsal hippocampus is additionally involved in orientation of movement and spatial navigation; whereas, the ventral hippocampus appears to be involved in limbic functions, social behaviors, motivation, stress responses, as well as neuroendocrine and autonomic functions (Behrendt, 2011; Fanselow and Dong, 2010; Gruber et al., 2010; Marquis et al., 2008; Roman and Soumireu-Mourat, 1988; Tseng et al., 2008). The majority of studies to date have focused on the role of the dorsal hippocampus in memory formation; however, an increasing number of studies are now focusing on the ventral hippocampus. As such, we will review studies focusing on both the dorsal and ventral hippocampus.

1.3. Cyclic nucleotides

Here, we focus on 3',5'-cyclic nucleotides, namely '3',5'-cyclic adenosine monophosphate' (cAMP) and '3',5'-cyclic guanosine monophosphate' (cGMP). Intracellularly, cAMP and cGMP act as second messengers, relaying signals from receptors on the cell surface to intracellular signaling cascades. Although the majority of studies examining the function of cyclic nucleotides focus on their role in intracellular signaling, it is important to keep in mind they are also found extracellularly where they serve a variety of important autocrine and paracrine functions (Ricciarelli and Fedele, 2018). As thoroughly reviewed elsewhere (Gurney, 2019), there are strong genetic associations between cyclic nucleotide signaling molecules and human cognitive performance, particularly among the enzymes responsible for degrading cyclic nucleotides. As we review below, both cAMP and cGMP appear to play an important role in hippocampal neuroplasticity and memory formation.

Previous reviews have focused primarily on the pharmacological manipulation of cyclic nucleotide signaling in the hippocampus (*e.g.*, (Heckman et al., 2018; Hollas et al., 2019; Prickaerts et al., 2017; Ricciarelli and Fedele, 2018), but here we will focus on studies utilizing genetic approaches. The reason for this is two-fold. First, cyclic nucleotide signaling is compartmentalized within discrete subcellular domains, with each domain regulated by a unique pool of synthesizing and degrading enzymes (Baillie et al., 2019). Although pharmacological studies have added to our understanding of the role cyclic nucleotide signaling plays in memory formation, they are limited in terms of spatiotemporal resolution because the pharmacological tools available today are not able to target the synthesizing and degrading enzymes in an isoform-specific manner—thus, multiple subcellular compartments of cyclic nucleotide signaling are modulated at once (Baillie et al., 2019). The second reason for focusing on studies using genetic techniques is that the neuroscience toolbox has significantly expanded in recent years with several genetic techniques (Deisseroth, 2015; Gorshkov and Zhang, 2014; Roth, 2016). These genetic techniques enable the measurement of real-time changes in cyclic nucleotide levels at the level of specific subcellular compartments, as opposed to measuring global changes in cyclic nucleotides that accumulate over time at the level of an entire brain region. They also enable the manipulation of cyclic nucleotide signaling in a subcellular compartment-specific manner. To provide a context for these genetic studies, we first offer an overview of cyclic nucleotide signaling in the hippocampus, including how cyclic nucleotides are generated by cyclases and hydrolyzed by phosphodiesterases (PDE) within discrete subcellular domains as well

as how cyclic nucleotides regulate neurotransmitter release and neuroplasticity. Subsequently, we review studies using genetic techniques to study the role of cyclic nucleotide signaling in memory formation, both studies measuring real-time changes in cyclic nucleotide levels and those manipulating signaling.

2. Molecular mechanisms of memory: a role for cyclic nucleotides in the hippocampus

2.1. Production of cyclic nucleotides

cAMP. The second messenger cAMP is synthesized from 'adenosine triphosphate' (ATP) by 'adenylate cyclase'. Adenylate cyclases can be divided into nine membrane-bound (or particulate) and one soluble adenylate cyclases (AC1-AC9). The membrane-bound adenylate cyclases are generally stimulated by G_s and inhibited by G_i and can be divided into four groups based primarily on their sensitivity and regulation by Ca^{2+} (Antoni et al., 1998; Paterson et al., 1995). Group I adenylate cyclases contains AC1, AC3 and AC8, which are activated by Ca^{2+}, group II contains AC2, AC4 and AC7 which are Ca^{2+}-insensitive, and group III consists of AC5 and AC6 which are inhibited by Ca^{2+}. Group IV is the exception and only contains AC9, which is non-responsive to forskolin and inhibited by calcineurin (CaN). Soluble adenylate cyclase is mainly located in the nucleus, mitochondria and centrosome during cell division and is activated by bicarbonate. Thus, roughly speaking, soluble adenylate cyclases respond to intrinsic cellular signals, whereas membrane-bound adenylate cyclases respond to extracellular signals (Zippin et al., 2003).

Expression of AC isoforms differs across hippocampal subfields and subcellular compartments. AC1 and AC2 are expressed in area CA1 and dentate gyrus, while AC8 is only expressed in CA1. In contrast, expression of AC5 and AC6 is largely restricted to the CA2 subregion. AC9 is the only isoform that is highly expressed in all three CA subregions and in the dentate gyrus (Antoni et al., 1998). AC1 and AC8 not only differ in terms of regional distribution, they also each display a unique pattern of subcellular localization. Whereas AC1 is abundantly expressed in the postsynaptic density and extrasynaptic sites, AC8 is mainly found in the presynaptic active zone and extrasynaptic fractions (Best et al., 2008). Thus, targeting different AC isoforms will modulate distinct subcellular domains within separable neural circuits, thereby differentially affecting memory formation.

cGMP. cGMP is also synthesized by both particulate and soluble cyclases that convert 'guanosine triphosphate' (GTP) into cGMP. Particulate guanylate cyclases are transmembrane enzymes that are activated by natriuretic peptides. In contrast to the particulate guanylate cyclase, that serves as a receptor for atrial, B-type and C-type natriuretic peptides, soluble guanylate cyclase is a receptor for gaseous ligands, especially nitrous oxide (NO) (Castro et al., 2006; Evgenov et al., 2006). NO is produced following activation of nitric oxide synthase (NOS) in response to increased Ca^{2+} (Murad et al., 1978). Soluble guanylate cyclase is typically found as a heterodimer, consisting of a larger α-subunit and a smaller haem-binding β-subunit, although it also exists as a homodimer (Zabel et al., 1999). Four human soluble GC subunits have been identified: α1, α2, β1 and β2. The α1/β1 and α2/β1 dimers (a.k.a. NO-GC1 and NO-GC2) are the most well-known, and exhibit indistinguishable catalytic, regulatory and pharmacological properties (Gibb et al., 2003; Russwurm et al., 1998).

The different human isoforms of soluble guanylate cyclase have been known for some time, however, little is published about their overall tissue distribution. In the hippocampus, NO-GCs are presynaptically localized in the excitatory and inhibitory axon terminals (Budworth et al., 1999; Burette et al., 2002; Peters et al., 2018; Szabadits et al., 2011). NO-GC2 also appears to be expressed postsynaptically via interactions with the PDZ domain-containing protein 'PSD-95' (Russwurm et al., 2001).

2.2. Breakdown of cyclic nucleotides

The compartmentalization of cyclic nucleotides is not only achieved by the distinct localization of the cyclases that generate them, but also by the differential anchoring of the various phosphodiesterase (PDE) isoforms that regulate their degradation (Baillie et al., 2019; Beavo, 1995; Conti and Beavo, 2007; Keravis and Lugnier, 2012; Lugnier, 2006; Maurice et al., 2014; Menniti et al., 2006). This compartmentalization of cyclic nucleotide signaling became apparent with the identification of A-kinase anchoring proteins (AKAPs) that tether PKA, PDEs and other proteins (Buxton and Brunton, 1983; Esseltine and Scott, 2013). PDEs are grouped into 11 families based on homology of their catalytic domains, with most families having more than one gene (Bender and Beavo, 2006). In total, there are estimated to be over a hundred specific human PDEs due to the fact that most genes encode several different splice variants (*i.e.* isoforms), each discretely localized to specific subcellular domains (Baillie et al., 2019; Houslay, 2010; Keravis and Lugnier, 2012; Kokkonen and Kass, 2017; Mongillo et al., 2004). Some PDEs specifically hydrolyze cAMP (PDE4, PDE7 and PDE8), others specifically hydrolyze cGMP (PDE5, PDE6 and PDE9), and the remaining families hydrolyze both cyclic nucleotides (PDE1, PDE2, PDE3, PDE10 and PDE11)(Francis et al., 2011). Several PDE families are allosterically modulated by cyclic nucleotides themselves constituting a feedback or feedforward mechanism (Francis et al., 2011). Specific inhibitors have been developed for every family of PDEs (Heckman et al., 2018), with several reaching the clinic for diseases such as erectile dysfunction, chronic obstructive pulmonary disease, and heart disease (Baillie et al., 2019; Maurice et al., 2014). Driven by these commercial successes, numerous PDE inhibitors have been investigated preclinically for memory-enhancing effects (Heckman et al., 2015b, 2017), with several yielding promising early results in clinical trials (Baillie et al., 2019; Heckman et al., 2018; Prickaerts et al., 2017; Heckman et al., 2015a, 2016).

2.3. Downstream signaling

In order for a given signaling event to regulate a specific physiological response, cyclic nucleotides must be regulated in a compartmentalized manner via signalosomes involving effector molecules (Conti et al., 2014; Maurice et al., 2014). Cyclic AMP has four main intracellular effectors, including 'exchange protein directly activated by cAMP' (Epac; a guanine nucleotide exchange factor for small G proteins such as Rap), PKA, cyclic nucleotide gated channels, and POPEYE-domain containing proteins (Baillie et al., 2019). Of these, Epac and PKA have been most studied in the context of hippocampus-dependent memory. The Epac family consists of two isoforms, 'Epac1' and 'Epac2'. The PKA family is comprised of four regulatory (RIα, RIβ, RIIα, RIIβ) and three catalytic (Cα, Cβ, Cγ) subunits resulting in the R subunit-based division of PKA into the 'PKAI' (consisting of RIα and RIβ dimers) and 'PKAII' classes (consisting of RIIα and RIIβ dimers). Both Epac and PKA can regulate multiple processes, ranging from receptor trafficking (*e.g.*, Song et al., 2013) to phosphorylation of the transcription factor 'cAMP response element binding protein' (CREB)(Abel and Nguyen, 2008; Pierre et al., 2009). Similarly, cGMP activates PKG, which exists in two forms, the soluble 'PKGI' and the membrane-bound 'PKGII' (Hofmann, 2005). Like PKA, PKG can also induce CREB activation by means of phosphorylation, thereby regulating transcription (Lu et al., 1999) (Fig. 2). The phosphorylation of CREB ultimately initiates transcription of a set of specific genes, including those encoding neurotransmitter receptors (*e.g.*, ionotropic AMPA receptors (Song et al., 2013) and growth factors (*e.g.*, 'brain-derived neurotrophic factor' (BDNF) (Scott Bitner, 2012).

2.4. Regulation of neurotransmitter release

In addition to regulating postsynaptic signaling events downstream

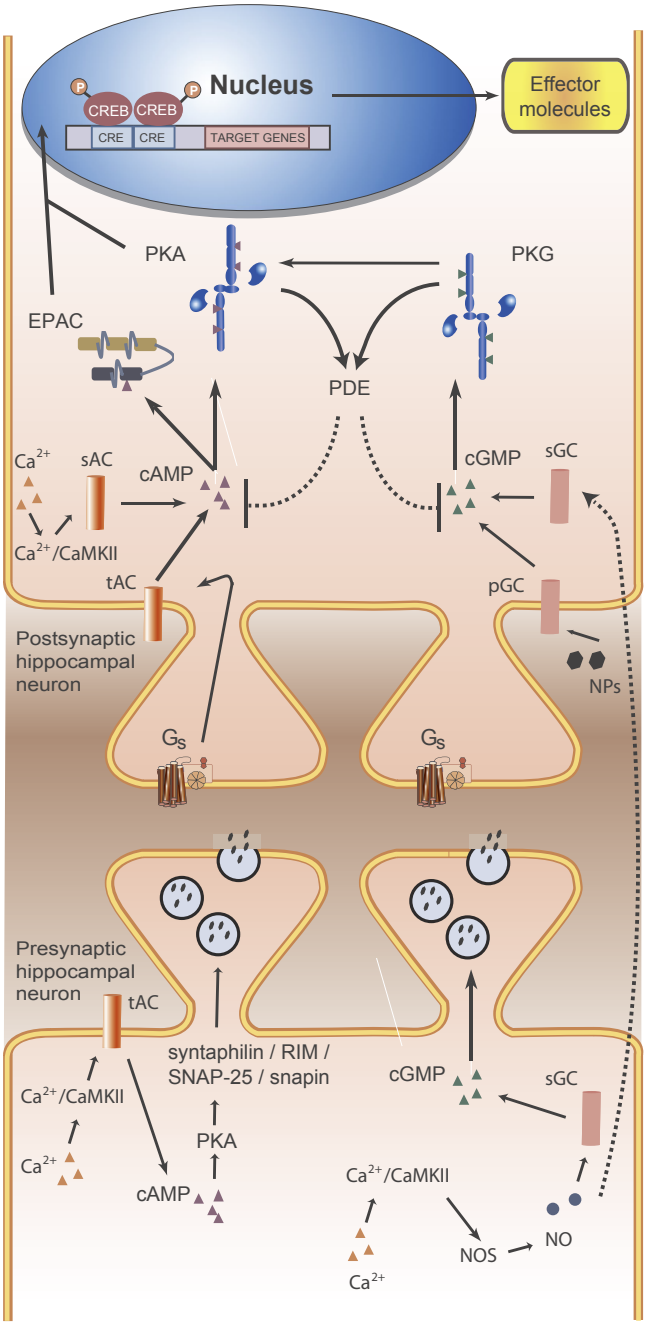

Fig. 2. Schematic diagram of pre- and postsynaptic cellular processes related to the second messengers cAMP and cGMP involved in neuroplasticity in the hippocampus. Presynaptically, both the cAMP and cGMP cascades can facilitate enhanced neurotransmitter release. Postsynaptically, both the cAMP/PKA and cGMP/PKG cascades activate several effectors including the transcription factor CREB. In turn, CREB initiates transcription of specific genes coding for multiple effector molecules including neurotransmitter receptors such as the ionotropic AMPA receptors, or growth factors as BDNF. Abbreviations: PDE = phosphodiesterase; Ca^{2+} = calcium; CaMKII = calmodulin-dependent protein kinase 2; NOS = nitric oxide synthase; NO = nitric oxide; pGC = particulate guanylate cyclase; sGC = soluble guanylate cyclase; cGMP = cyclic guanosine monophosphate; PKG = protein kinase G; tAC = transmembrane adenylate cyclase; sAC = soluble adenylate cyclase; cAMP = cyclic adenosine monophosphate; PKA = protein kinase A; Epac = Exchange protein activated by cAMP; NPs = natriuretic peptides; Gs = stimulatory G protein; CREB = cAMP response element binding protein; Cre = cAMP response elements.

of G-protein-coupled receptors (GPCR), cAMP can also regulate events presynaptically. Adenylate cyclase that is present in the presynaptic terminal is activated by (Ca^{2+})/calmodulin-dependent protein kinase (CaMKII). This, in turn, leads to increased cAMP synthesis and activation of PKA. PKA can then stimulate docking, priming, and fusion of presynaptic vesicles to the membrane by phosphorylating syntaphilin and SNAP-25, Rab3 interacting molecule (RIM) and snapin, and cysteine string protein (CSP), respectively (Leenders and Sheng, 2005). Similarly, presynaptic production of cGMP can be stimulated by the retrograde messenger NO and, thus, regulate phosphorylation events via activation of PKG. Thus, both a presynaptic CaMKII/cAMP/PKA cascade (Bayer and Schulman, 2019) and a presynaptic NO/cGMP/PKG cascade can regulate the synthesis, metabolism and release of neurotransmitters, including glutamate and dopamine (Cheng et al., 2018a,b; Imanishi et al., 1997; Nishi and Snyder, 2010; Ohi et al., 2019; Rodriguez-Moreno and Sihra, 2013; Schoffelmeer et al., 1985;Arancio et al., 1995; Sanchez et al., 2002; Wang et al., 2017a) (Fig. 2). Acquisition processes, short-term memory and, possibly, long-term memory may be related, in part, to changes in neurotransmitter release that are orchestrated by these cyclic nucleotide signaling pathways (Akkerman et al., 2014, 2015).

2.5. Regulation of neuroplasticity

Both the cAMP/PKA/CREB and the cGMP/PKG/CREB pathways are implicated in long-term potentiation (LTP), a proposed neurophysiological correlate of memory (Bliss and Collingridge, 1993; Frey et al., 1993; Lu et al., 1999). LTP can be induced and measured both *in vitro* and *in vivo*, when a moderately high frequency stimulation produces a stable and lasting increase in synaptic responses (Bliss and Collingridge, 1993; Reymann and Frey, 2007). A distinction is made between two different types of hippocampal LTP (Ricciarelli and Fedele, 2018). Early-phase LTP (E-LTP) lasts less than three hours, while late-phase LTP (L-LTP) lasts 3 h or longer. Furthermore, it has been suggested that E-LTP resembles early consolidation processes, while L-LTP is involved in late consolidation processes in long-term memory (Bollen et al., 2015, 2014; Heckman et al., 2017). A presynaptic cGMP/PKG pathway (Arancio et al., 1996) as well as postsynaptic cGMP/PKG pathway have been implicated in E-LTP (Taqatqeh et al., 2009). In contrast, cAMP/PKA signaling appears not to be involved in E-LTP (Abel et al., 1997; Bollen et al., 2015, 2014). A postsynaptic cAMP/PKA/CREB pathway as well a postsynaptic cGMP/PKG/CREB pathway are essential for L-LTP (Abel et al., 1997; Impey et al., 1996)(Lu et al., 1999) (Fig. 2). Interestingly, early phase cGMP/PKG signaling has been shown to require late-phase cAMP/PKA-signaling in L-LTP and long-term memory (Bollen et al., 2014), suggesting that crosstalk between these signaling pathways exists (Fig. 2).

3. Optical biosensors for measuring real-time changes in cyclic nucleotide levels

Changes in cyclic nucleotide levels are traditionally measured with biochemical techniques like radiolabel- and immuno-assays, which can give a relative estimation of the amount of cAMP or cGMP in cell lysates. Drawbacks of these approaches include a requirement for large amounts of cells/tissue and, more importantly, a lack of spatiotemporal resolution for measuring real-time changes in cyclic nucleotide gradients in living cells. The development of optical biosensors based on Förster resonance energy transfer (FRET), bioluminescence resonance energy transfer (BRET), or single fluorescent proteins significantly improved our ability to measure and monitor cyclic nucleotide dynamics (Sprenger and Nikolaev, 2013)(Fig. 3).

3.1. FRET-based biosensors for detecting cAMP

The first biosensors for detecting changes in intracellular cAMP

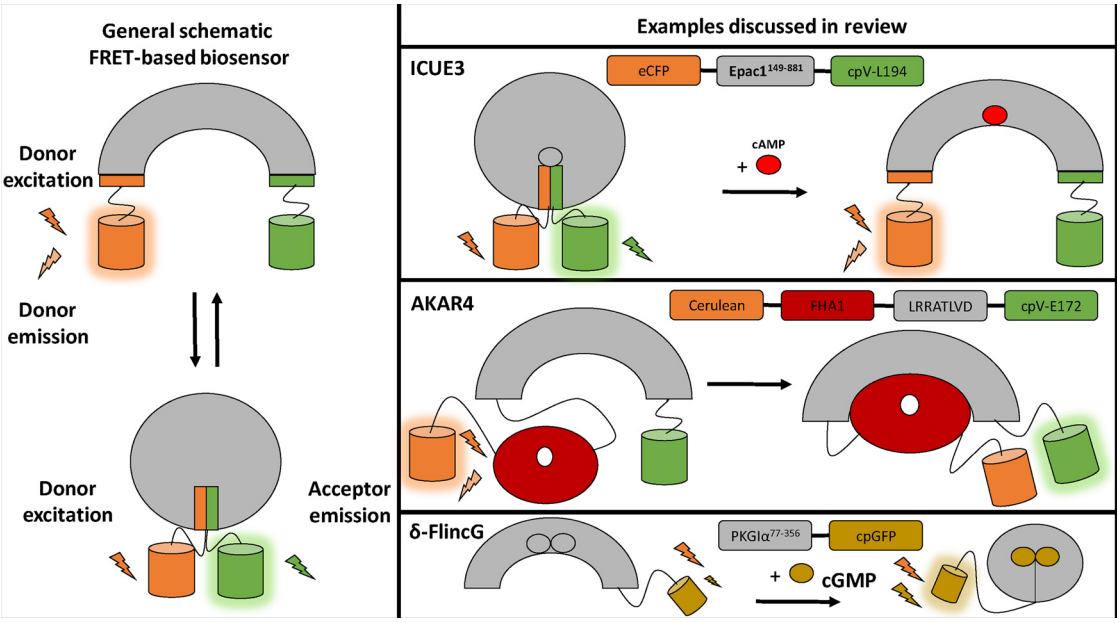

Fig. 3. Design of cyclic nucleotide biosensors including the general design and examples discussed in the current review. ICUE3 (indicator of cAMP using EPAC version 3) is an EPAC-based biosensor to measure changes in cAMP levels. It consists of an Epac$^{1149–881}$ sensing unit, eCFP donor, and a cpV-L194 acceptor reporting unit. When cAMP binds to this sensor, it switches from high to low fluorescence emission. AKAR4 belongs to the family of biosensors that contain a PKA substrate sequence and a phospho-binding domain sandwiched between 2 fluorescent proteins (Cerulean donor and cpV-E172 acceptor) for measuring PKA activity. Increased PKA activity leads to phosphorylation of the PKA substrate and subsequent binding to the phospho-domain increasing FRET. δ-FlincG is used to detect changes in cGMP gradients and contains, in contrast to most other sensors, a truncated cGMP binding domain from PKGIα or PKGIβ flagged with a single circularly-permuted enhanced GFP, which increases the fluorescence emitted upon binding of cGMP (based on Gorshkov and Zhang, 2014).

levels were based on cAMP itself and made use of the dissociation of the catalytic and regulatory subunits of PKA upon cAMP binding. 'FlCRhR' (Fluorescein-labeled PKA Catalytic subunit and Rhodamine-labeled Regulatory subunit) was the first cAMP biosensor and comprised a fluorescein-tagged catalytic subunit and a rhodamine-labeled regulatory subunit. Binding of cAMP to the regulatory subunit caused its dissociation from the catalytic subunit leading to a reduction in FRET emission (Adams et al., 1991). A few years later, Zaccolo and colleagues developed a genetically-encoded cAMP biosensor in which the catalytic or the regulatory subunit of PKA were fused with a fluorescent probe (Zaccolo et al., 2000). FlCRhR proved useful in unraveling cAMP signaling dynamics and compartmentalization in rat cardiac myocytes (Zaccolo and Pozzan, 2002) and provided information about the spatial distribution of cAMP/PKA during stimulation of sensory neurons in *Aplysia* (Bacskai et al., 1993). Unfortunately, the use of this tool was limited because of the need for equal expression of both recombinant subunits and the potential interference of endogenous PKA subunits.

Challenges of the PKA-based detectors were overcome by the development of singled-chained Epac-based biosensors that took advantage of the fact that cAMP induces a conformational change in Epac upon binding. Both Epac1 and Epac2 were fused with cyan-fluorescent protein (CFP) at the N-terminus and yellow-fluorescent protein (YFP) at the C-terminus. In absence of cAMP, Epac biosensors remain in the "closed" state. Thus, laser stimulation of the CFP generates an emission spectrum that is capable of stimulating the YFP. Upon cAMP binding, however, Epac "opens up". Thus, the CFP is no longer close enough to stimulate the YFP, resulting in a decrease in this FRET emission (DiPilato et al., 2004; Nikolaev et al., 2004; Ponsioen et al., 2004). Next, this Epac1 biosensor was fused to the N-terminal domain of different PKA subunits resulting in PKA-RI- and PKA-RII-specific FRET biosensors (Wachten et al., 2010). In rat myocytes, these PKA-RI and PKA-RII biosensors revealed a microdomain-specific regulation of cAMP levels mediated through specific PDEs (Stangherlin et al., 2011). For instance, stimulation of the β-adrenoceptor generates a spatially-restricted pool of cAMP that mainly activates PKA-RII and to lesser extent PKA-RI. Subsequent cGMP production via stimulation of soluble guanylate cyclase promotes activation of PDE2 that is in close proximity to the PKA-RII pool and inhibition of PDE3 that resides close to PKA-RI, thus, reversing the PKA-defined cAMP gradient (Stangherlin et al., 2011). Additionally, Epac2 biosensors tagged to AC8 (Epac2AC8^{D416N}) helped to identify distinct pools of cAMP microdomains associated with adenylate cyclase activity in pituitary cells (Wachten et al., 2010). Interestingly, the transgenic mouse line 'GAG-Epac1-camps' that expresses an EPAC1 biosensor ubiquitously allows detection of cAMP signaling in a more physiological context (Calebiro et al., 2009).

The most well-known EPAC-based probes are called 'ICUE' (indicator of cAMP using EPAC). Three versions have been developed (ICUE1-3), each containing progressively improved properties (*e.g.*, increases in dynamic range) that facilitate subcellular targeting (DiPilato et al., 2004; Liu et al., 2012; Marley et al., 2013). ICUE1 constructs that were modified for trafficking to the plasma membrane, mitochondria, and nucleus of HEK-293 cells revealed the differential dynamics and propagation of cAMP signaling that exist within these subcellular compartments following adrenergic stimulation (DiPilato et al., 2004). ICUE2 is a biosensor like ICUE1, that has a membrane- and mitochondria-targeting sequence removed from the N-terminus of the Epac1 sequence, thereby exhibiting improvement in localization compared to ICUE1 (Violin et al., 2008). ICUE3 probes targeted to the nucleus showed that the nuclear PKA holoenzyme promotes signaling in response to activated soluble adenylate cyclase (Hotte et al., 2012). Additionally, utilization of the ICUE3 probe revealed a novel role of the actin binding protein 'coronin 1' in modulating synaptic plasticity and neurobehavioral processes via potentiation of the cAMP/PKA pathway (Jayachandran et al., 2014).

An alternative approach to detect cAMP signaling is via the 'A-kinase activity reporter' (AKAR). This family of biosensors contains a PKA substrate sequence and a phospho-binding domain sandwiched between 2 fluorescent proteins. Increased PKA activity leads to phosphorylation of the PKA substrate and subsequent binding to the phospho-domain increasing FRET. Where most previous biosensor

studies were conducted in cell cultures with a focus on cardiac function, the AKAR-based biosensors have also been used to detect real-time changes in cAMP gradients in brain slices (*e.g.*, Castro et al., 2014). For example, biosensor imaging in mouse brain slices showed that cAMP/PKA signaling differs between striatal and cortical neurons (Castro et al., 2013). Striatal neurons exhibit faster and longer-lasting responses to stimuli that elevate cAMP/PKA levels compared to cortical neurons due to several parameters including enhanced PDE4 activity in the cortex and stronger adenylate cyclase activation in the striatum (Castro et al., 2013). Another example comes from Tang and colleagues who used the 'AKARet-cyto' biosensor to image PKA activation in single dendritic spines during structural LTP in hippocampal CA1 pyramidal neurons, revealing that the activation of this kinase spreads widely with length constants of more than 10 μm (Tang and Yasuda, 2017).

3.2. FRET-based biosensors for detecting cGMP

For the detection and measurement of real-time changes in cGMP gradients, similar biosensors have been developed for cGMP. cGMP biosensors have to be highly sensitive due to the low concentrations of cGMP in neurons. This need for high sensitivity has proven challenging. cGMP biosensors are based on the fusion of a cyclic nucleotide binding domain derived from PKG or cGMP-specific PDEs between two fluorophores. The first PKG-based biosensors were the cygnet (cyclic GMP indicator using energy transfer) series of cGMP biosensors (Honda et al., 2001). The first biosensor, called 'Cygnet-1', was comprised of a truncated version of PKGIα flanked between CFP and YFP at the N-terminus and C-terminus, respectively; whereas, Cygnet-2 was the catalytically inactive variant of Cygnet-1 due to a PKG1α-T516A mutation (Honda et al., 2001). With both Cygnet probes, binding of cGMP leads to a decrease in FRET (Sato et al., 2000). Sato et al. also generated a PKG1α-based probe called 'CGY-Del1' that responded to cGMP binding with an increase in FRET (Sato et al., 2000). The Cygnet biosensors have contributed to our understanding of the spatiotemporal dynamics of cGMP in various cell types (Cawley et al., 2007; Mongillo et al., 2006; Takimoto et al., 2005). Regarding neural systems, cygnet biosensors have shown that basal cGMP concentrations in thalamic neurons are mainly regulated by PDE2 activity, even though they express PDE1, PDE2, PDE9 and PDE10 as well (Gervasi et al., 2007). Furthermore, cygnet was used in combination with an EPAC-based sensor (EPAC-SH^{150}) to show that cGMP signaling can reduce cAMP signaling through activation of PDE2 in striatal medium spiny neurons (Polito et al., 2013).

Although these first generation cGMP biosensors shed new light on cGMP signaling in the nervous system, they were still characterized by a low dynamic range and limited temporal resolution. As a result, three shorter cGMP biosensors were developed containing a single cGMP-binding domain from PKGIα (cGES-GKIB), the GAF domain from PDE2A (cGES-DE2), or the GAF domain from PDE5A (cGES-DE5) (Nikolaev et al., 2006). Binding of cGMP decreases the FRET signal in case of the PKGIα-based biosensor, while the FRET signal increases in the case of PDE-based biosensors. All three cGMP biosensors show strong FRET responses, however cGES-DE5 clearly has the greater selectivity of cGMP over cAMP and is therefore the preferred sensor for neuronal (live-cell) tissue (Gorshkov and Zhang, 2014). Two versions of the same cGMP biosensor were used for simultaneous imaging of both cAMP and cGMP in the same cell by substituting CFP/YFP by a red (Dimer2) and green (T-Sapphire) fluorescent protein (Niino et al., 2009). This drastically increased the affinity making it potentially suitable for measuring low concentrations of cGMP. The fluorescent indicators for cGMP (FlincGs) line of biosensors was also seen as an improvement. The FlincGs (α-FlincG, β-FlincG, and δ-FlincG) contain a truncated cGMP binding domain from PKGIα or PKGIβ flagged with a circularly-permuted enhanced GFP, which increases the fluorescence emitted upon binding of cGMP (Nausch et al., 2008). Finally, a blue single-color cGMP sensor called 'Cygnus' was developed containing the GAF-A domain of PDE5 fused between a blue fluorescent donor and a dark fluorescent acceptor, which was able to detect cGMP signaling in rat hippocampal neurons (Niino et al., 2010). In addition, Russwurm and colleagues generated the cGi-500, cGi-3000, and cGi-6000 cGMP biosensors with faster kinetics and a wide range of affinities by using the tandem CNBD domains of PKGIα as a sensing unit (Russwurm et al., 2007). They started out with the indicator CFP-PKGIα79–336-YFP, elongated the N- and C-termini, and subsequently screened the constructs based on their affinity for cGMP and FRET response.

Clearly, cyclic nucleotide FRET-based biosensors have been dramatically improved in recent years (for an elegant overview see Gorshkov and Zhang, 2014). The use of first-generation cGMP biosensors to study memory-related processes at a cellular level has been particularly limited by the fact that cGMP levels are so much lower than cAMP levels in neurons. That said, more recent technical advances have further improved the sensitivity and increased the dynamic range of both the cAMP and cGMP biosensors. As a result, we are now seeing the first reports emerge examining striatal signaling and excitability as well as hippocampal synaptic plasticity (Muntean et al., 2018). For instance, Muntean et al. used a newly developed cAMP sensor called 'TEpacVV' (Klarenbeek et al., 2011), which was placed under control of a chicken-actin-G promoter and preceded by a STOP cassette flanked by LoxP sites. The latter enabled the researchers to conditionally express the sensor in a Cre recombinase-dependent fashion in any brain region and cell type of interest of the mutant mice. This sensor uses mTurquoise as donor providing double quantum efficiency and only single-exponential fluorescent decay when compared to CFP described above (Muntean et al., 2018; Calamera et al., 2019). Tang and Yasuda (2017) recently developed a novel sensor that measures PKA protein content with extremely high spatial resolution. More specifically, this sensor has sufficient sensitivity to detect changes in PKA gradients in small neuronal compartments such as dendritic spines, something that was not possible with other sensors

3.3. BRET-based biosensors

BRET is another, more recent form of biosensor used for imaging protein association inside living cells. In case of BRET, a bioluminescent molecule acts as energy donor, while for FRET both the donor and acceptor are fluorescent molecules. Biswas and colleagues (Biswas et al., 2008) developed a cGMP BRET biosensor for cGMP based on the FRET-based biosensor described above (Niino et al., 2009). This BRET biosensor utilized the GAF domain of the cGMP-binding PDE5 and enabled researchers to show that these GAF domains act as an intracellular sink for cGMP molecules, and could be used to identify allosteric modulators that bind to the GAF domain of PDE5.

3.4. Single fluorescent protein-based indicators for cAMP

Single fluorescent protein (1-FP)-based indicators have also been developed. In comparison to the FRET or BRET biosensors, these indicators utilize the exchange of ionization states in the chromophore of a single fluorescent protein. The rationale for using these single fluorescent proteins is that the fluorescent intensity heavily depends on the direct environment of the protein. Any conformational change will lead to a slight change in the environment resulting in altered fluorescent intensity (Matsuda et al., 2017). Using this approach, Flamindo2 (Odaka et al., 2014) was generated by inserting the Epac1 cAMP binding domain into the middle of the YFP variant, citrine. Flamindo2 was reported to exhibit an increased dynamic range that was capable of detecting very strong artificially induced cAMP responses (*e.g.*, in response to, for instance, forskolin). Pink Flamindo27, a red color variant of Flamindo2 consisting of mApple, allowed advanced applications, including *in vivo* imaging and optogenetic manipulations (Harada et al., 2017). The affinity of 1-FP-based indicators for cAMP can be increased by replacing the low-affinity EPAC cAMP binding domain with that of

the high-affinity PKA regulatory subunits cAMP binding domain (*e.g.*, Harada et al., 2017). Thus, Ohta and colleagues increased affinity and expanded the dynamic range of their red fluorescent cAMP 1-FP indicator termed 'R-FlincA' by inserting an mApple variant, cp146mApple, into the high-affinity cAMP-binding motif of the PKA R1α subunit (Ohta et al., 2018).

3.5. Single fluorescent protein-based indicators for cGMP

A single fluorescent protein-based indicator has also been developed for cGMP, called 'Green cGull' (Matsuda et al., 2017). Green cGull is based on the cGMP-binding domain of PDE5 inserted in the vicinity of the chromophore Citrine, a green fluorescent protein. Binding of cGMP will result in a conformational change of the fluorescent protein leading to an increase in fluorescent intensity.

4. Genetic approaches for manipulating cyclic nucleotide signaling

Genetic approaches used to manipulate cyclic nucleotide signaling for the study of memory have dramatically evolved over the course of recent decades. The majority of studies have employed conventional knockout mice (KOs) and/or transgenic mice expressing/overexpressing a "normal" enzyme, dominant negative enzyme, or a molecule designed to disrupt subcellular localization of an enzyme. More recent studies, however, have used chemogenetic and optogenetic approaches to more precisely manipulate cyclic nucleotide signaling within discrete cell populations and/or neural circuits. Although studies using conventional KO mice suffer from several limitations (*e.g.*, potential for compensatory upregulation of other signaling molecules, failure to target one specific protein isoform, etc.), they have advanced our knowledge of how cyclic nucleotide signaling regulates learning and memoryand synaptic plasticity. Here we review studies that have genetically manipulated cyclases, PDEs, or cyclic nucleotide effector molecules.

4.1. Genetic manipulation of adenylate cyclases

4.1.1. AC1 and AC8

The majority of studies targeting ACs have focused on AC1 and AC8. Although a recent review suggests neither AC1 nor AC8 are genetically associated with cognitive performance in humans generally speaking (c.f., (Gurney, 2019)), functional studies suggest an important role for these enzymes specifically in hippocampal plasticity and memory. Early work showed that genetic mutation of AC1 impaired induction and maintenance of mossy fiber LTP (dentate gyrus→CA3; Villacres et al., 1998) as well as induction—but not maintenance—of long-lasting Schaffer collateral LTP (CA3→CA1; Wu et al., 1995). In contrast, induction and maintenance of early Schaffer collateral LTP and perforant path LTP (entorhinal area→dentate gyrus) were unaffected by the loss of AC1 signaling (Villacres et al., 1998). When AC1 was transgenically overexpressed throughout the forebrain, Schaffer collateral LTP was strengthened (*i.e.*, an early LTP protocol was able to induce long-lasting LTP; Wang et al., 2004), while long-term depression was impaired, and synaptic depotentiation remained intact in this pathway (Wang et al., 2004; Zhang and Wang, 2013). These selective effects of AC1 manipulations on mossy fiber and Schaffer collateral LTP/LTD are consistent with the fact that 1) the Ca^{2+}-stimulated AC1 is expressed in the dentate gyrus and CA3 pyramidal cells, 2) induction of mossy fiber and long-lasting Schaffer collateral LTP require Ca^{2+} (Kumar, 2011; Yeckel et al., 1999) and cAMP/PKA signaling (Villacres et al., 1998), and 3) mossy fiber LTP can be induced by forskolin (Villacres et al., 1998). AC8 knockout mice also show deficits in mossy fiber LTP, but not early Schaffer collateral LTP (Wang et al., 2003). Interestingly, mossy fiber LTP deficits caused by deletion of AC8 are equivalent to deficits caused by deletion of AC1, and deletion of both AC1 and AC8 does not further exacerbate these LTP deficits (Wang et al., 2003). In contrast, whereas the loss of either AC1 or AC8 does not affect long-lasting Schaffer collateral LTP, depletion of both does impair the maintenance thereof (Wong et al., 1999; Zhang et al., 2001). Given that AC8 deletion did not affect Schaffer collateral LTP, it is surprising that transgenic restoration of only AC8 throughout the forebrain was sufficient to rescue the Schaffer collateral LTP deficits that were observed in the double knockout (Wieczorek et al., 2012). Depletion of both AC1 and AC8 also impairs long-term depression and synaptic de-potentiation (*i.e.*, the reversal of LTP) in this pathway (Wong et al., 1999; Zhang et al., 2011). Together, these findings suggest that both AC1 and AC8 are important for bidirectional synaptic plasticity. The fact that the effects of AC8 deletion plus AC1 loss of function are non-additive in some instances (e.g., impairing mossy fiber LTP), yet synergistically interact in other instances (*e.g.*, impairing maintenance of Schaffer collateral LTP), may be explained in part by the differential distribution of these two Ca^{2+}-stimulated adenylate cyclases across hippocampal subregions (Conti et al., 2007).

AC1 and AC8 are also critical for formation and retrieval of hippocampus-dependent memories. Mutation of AC1, but not AC8, impairs memory retrieval in the visible and hidden platform water mazes (Wu et al., 1995; Zhang et al., 2008b). Loss of both AC1 and AC8 function also impairs memory in the hidden platform water maze, as it does the ability to suppress previous memories of platform locations and form memories for new locations (*i.e.*, reversal learning; Zhang et al., 2011). In contrast, overexpression of AC1 throughout the forebrain improves the rate at which young adult mice acquire intial hidden platform locations as well as their reversal learning performance (Zhang and Wang, 2013), but does not affect their long-term memory for the intial platform location (Garelick et al., 2009). Interestingly, this type of spatial memory is actually impaired by AC1 overexpression in old mice (Garlick et al., 2009). Long-term social recognition memory is also differentially affected by AC1 overexpression depending on the age of the mice. Whereas young adult mice show stronger long-term memory in response to AC1 overexpression, old mice show no effect (Garelick et al., 2009). The fact that AC1 overexpression does not improve memory in aged mice may appear counterintuitive considering the fact that AC1 activity is downregulated with age in the hippocampus (Garelick et al., 2009). That said, this downregulation may reflect a compensatory protective mechanism in response to changes elsewhere in the signal transduction cascade. Indeed, basal cAMP levels are not thought to change with age in the hippocampus as they do in other brain regions like prefrontal cortex (c.f., (Kelly, 2018a)). Alternatively, the lack of positive effect in these hippocampus-dependent tasks may be related to a deleterious influence of AC1 overexpression outside of the hippocampus, particularly in the prefrontal cortex where cAMP levels and PKA activity are already increased with age due to a downregulation of PDE4 (Arnsten et al., 2005; Ramos et al., 2003). Together, these findings suggest that the role of cyclic nucleotide signaling in hippocampus-dependent memory may evolve across the lifespan.

AC1 and AC8 affect other types of hippocampus-dependent memories as well. Mutation of either AC1 or AC8 is not sufficient to impair recent long-term memory in a standard paradigm for passive avoidance nor contextual fear conditioning (Wong et al., 1999). That said, deletion of both AC1 and AC8 does impair recent memory for standard passive avoidance (Wong et al., 1999), and deletion of AC8 along impairs memory in a modified passive avoidance paradigm that employs temporal dissociation (Zhang et al., 2008). This pattern of behavioral phenotypes is similar to that described above for LTP where deletion of either AC1 or AC8 was sufficient to impair mossy fiber LTP but deletion of both was required to impair both the induction and maintenance of Schaffer collateral LTP. Also in parallel with the LTP findings described above, overexpression of AC1 was able to convert a short-term memory training protocol into a long-term object memory (Wang et al., 2004). Although AC1 mutant mice exhibit normal recent long-term memory for contextual fear memory, they demonstrate impaired remote long-

term memory 11 weeks after training when compared to wild-type mice (Shan et al., 2008). The timing of this remote memory deficit is expedited when both AC1 and AC8 function are lost, with deficits in contextual fear conditioning observed even at 7–8 days after training (Wong et al., 1999; Wieczorek et al., 2012). Further, double knockout mice fail to show enrichment-induced increases in contextual fear memory 7 days after training, as do wild-type mice (Wieczorek et al., 2012). Consistent with these findings, transgenic mice overexpressing AC1 show normal recent long-term memory for contextual fear conditioning yet an enhanced remote long-term memory 22 weeks after training (Shan et al., 2008). This enhanced remote LTM is associated with an impaired ability to extinguish the memory as well as increased ERK and CREB phosphorylation (Wang et al., 2004). Together, these findings point towards an important role for AC1 and AC8 in the formation and stabilization of hippocampus-dependent memories.

4.1.2. AC3

Limited evidence also implicates AC3, a Ca2+-inhibited AC, as playing a role in hippocampus-dependent memory. AC3 exhibits a very unique expression pattern, with a discrete enrichment in primary neuronal cilia (Bishop et al., 2007; Wang et al., 2011). Although the exact role that neuronal cilia play in neuroplasticity and memory formation remains to be elucidated, it is hypothesized that cilia represent receptor signaling platforms (Green and Mykytyn, 2014). Similar to the AC8 knockout mice described above, AC3 knockout mice show normal memory in a standard passive avoidance assay, impaired memory in a temporally-dissociated passive avoidance paradigm, and impaired object recognition memory (Wang et al., 2011; Wong et al., 2000; Zhang et al., 2008). Although AC3 KO mice demonstrate normal memory for contextual fear conditioning, they fail to extinguish the memory (Wang et al., 2011). This finding stands in contrast to that reported for AC1 mutant mice, which show intact extinction of contextual fear conditioning (Shan et al., 2008). Thus, AC1, AC3, and AC8 appear to have overlapping, yet distinct, roles to play in neuronal plasticity and memory formation.

4.1.3. AC6

AC6, another Ca2+-inhibited AC, may also contribute to hippocampal function. Perhaps counterintuitively, genetic deletion of AC6 increases expression and phosphorylation of CREB within hippocampal neuron nuclear fractions as well as expression and phosphorylation of the NMDA receptor subunit GluN2B in hippocampal neuron synaptosomal fractions (Chang et al., 2016). Interestingly, the effect of AC6 on CREB levels is independent of AC6 catalytic activity (Chang et al., 2016), suggesting the loss of AC6 fundamentally alters protein-protein binding interactions within a specific macromolecular complex. In concert with these biochemical effects, AC6 knockout mice exhibited an increased ratio of NMDAR-mediated vs. AMAPR-mediated EPSCs, stronger NMDA-dependent Schaffer collateral LTD, enhanced spatial learning and reversal learning (although equivalent short-term spatial memory) in the MWM, and stronger short-term memory for contextual fear (Chang et al., 2016).

Together, these data have greatly contributed to our understanding of how adenylate cyclases regulate memory formation. That said, they also underscore the importance of moving toward more regionally-selective manipulations in future studies. This may be accomplished by utilizing cell-type specific promoters in combination with brain-region specific injections of viral constructs. Ideally, promotors should be selected that preferentially target a specific hippocampal sub-region, as different sub-regions may be active during specific types of memory (spatial vs non-spatial) and memory processes (acquisition, consolidation, retrieval) (Havekes et al., 2007).

4.2. Genetic manipulation of guanylate cyclases

Only a handful of studies have examined the role of either soluble or particulate guanylate cyclases in hippocampal function using genetic approaches. With regard to soluble guanylate cyclases, NO-GC1 and NO-GC-2 have been most studies. Electrophysiological and immunofluorescence analysis localized NO-GC1 to the presynaptic compartment and NO-GC2 to the postsynaptic compartment of glutamatergic neurons in the hippocampus (Neitz et al., 2011, 2014; Neitz et al., 2015). Deletion of either NO-GC isoform completely abolished LTP in the visual cortex and hippocampal CA1 synapses (Haghikia et al., 2007; Taqatqeh et al., 2009). These LTP deficits may be related to the fact that NO-GC1 regulates glutamate and GABA release within CA1, and NO-GC2 increases postsynaptic responsiveness of glutamatergic neurons (Neitz et al., 2011, 2014; Neitz et al., 2015). Unfortunately, to our knowledge no studies have been published that examine hippocampus-dependent behaviors in these mouse lines. The only behavioral study to date suggests that a loss of NO-GC1 from spinal dorsal horn neurons leads to reduced hypersensitivity in models of neuropathic, but not inflammatory pain; whereas, the loss of NO-GC2 from these same neurons leads to increased hypersensitivity in models of inflammatory but not neuropathic pain (Petersen et al., 2019). Although studies that genetically manipulate guanylate cyclase are sparse, results to date indicate an important role for soluble guanylate cyclases in neuroplasticity. These findings also underscore the importance for targeting manipulations in a region, cell-type, and even subcellular compartment-specific manner.

Only one study to date has examined the role of particulate guanylyl cyclases in hippocampal function. Genetic deletion of GC-C impaired short-term memory for novel object recognition, but recent long-term memory for contextual fear conditioning was normal as was spatial learning, spatial memory, and reversal learning in the MWM (Mann et al., 2019). Consistent with this display of intact hippocampus-dependent memory, serotonin and norepinephrine levels were unchanged in GC-C knockout mice relative to wild-type mice (Mann et al., 2019). Together, these data argue against a pervasive role of GC-C in hippocampal function.

4.3. Genetic manipulation of phosphodiesterases

4.3.1. Phosphodiesterase 1

PDE1 is a Ca^{2+}-dependent, dual substrate cyclic nucleotide PDE and this family of enzymes includes three genes PDE1A, PDE1B and PDE1C (Beavo, 1995; Wennogle et al., 2017). PDE1C in particular has been genetically associated with cognitive performance in humans (c.f., (Gurney, 2019)), and a balanced de novo inversion disrupting PDE1C has been associated with developmental delay (Gamage et al., 2013). Tools for genetically manipulating PDE1A, PDE1B, and PDE1C exist (*e.g.*, Cygnar and Zhao, 2009; Wang et al., 2017b; Ye et al., 2016); however, only those targeting PDE1B have been used in the study of hippocampal function. In both the passive avoidance and conditioned avoidance tests, PDE1B knockout mice performed similarly to wild-type mice (Siuciak et al., 2007b). In contrast, homozygous PDE1B (-/-) and heterozygous PDE1B (+/-) knockout mice demonstrated spatial learning and memory deficits in the hidden platform Morris water maze (MWM) task when trained and tested as adolescents (postnatal day 50; Reed et al., 2002). When tested as adults (postnatal day 85), however, PDE1B homozygous KO mice showed intact spatial learning and memory but impaired reversal learning in the MWM (Ehrman et al., 2006). Surprisingly, viral knockdown of PDE1B in young adult mice (3–6 months old) that was restricted to the CA fields of hippocampus actually enhanced contextual fear conditioning memory and spatial memory in the Barnes maze without effecting non-cognitive behaviors (McQuown et al., 2019). Thus, local deletion in the hippocampus improved memory function; whereas, general knockdown of the same gene across brain regions impaired memory processes. PDE1B is known to be expressed in cortical (Pekcec et al., 2018) and striatal (Nishi and Snyder, 2010) neurons where it is tightly linked to dopamine receptor function. Effects of PDE1B deletion on striatal functions, such as

locomotion and reward processing, may partly explain the discrepancy between localized versus global manipulations of PDE1B signaling when considering hippocampal output.

4.3.2. Phosphodiesterase 4

The PDE4 family is cAMP-specific and encoded by 4 different genes, PDE4A, PDE4B, PDE4C and PDE4D (Beavo, 1995; Houslay and Adams, 2003; O'Donnell and Zhang, 2004; Prickaerts et al., 2017). Only PDE4A, PDE4B and PDE4D are expressed in the rodent and human brain (Kelly et al., 2014; Lakics et al., 2010). Although multiple studies have genetically associated PDE4B and PDE4D with human cognitive performance in general (c.f., (Gurney, 2019) or mental disorders associated with wide-ranging cognitive impairments (e.g., (Fatemi et al., 2008; Lee et al., 2012; Linglart et al., 2012; Lynch et al., 2013; Michot et al., 2012; Millar et al., 2005)), evidence to date largely points to PDE4A and PDE4D playing the largest role in specifically regulating hippocampus-dependent memories.

4.3.2.1. PDE4A. PDE4A knockout mice have been extensively characterized to date. Relative to wild-type mice, PDE4A knockout mice exhibit improved passive avoidance memory yet normal object recognition memory and spatial memory as assessed in the MWM (Hansen et al., 2014). The selective effect on passive avoidance memory may be related to the aversive nature of the stimuli employed in this particular paradigm coupled with the fact that deletion of PDE4A appears to be anxiogenic as measured by the elevated-plus maze, light-dark transition, and novelty-suppressed feeding tests. As extensively reviewed elsewhere (Baillie et al., 2019), each PDE(4) isoform is anchored to a unique set of protein complexes through its N-terminal domain thereby leading to targeted degradation of cAMP in specific intracellular compartments. Isoform-specific mutant mice have not yet been published; however, studies employing viral vector approaches are now emerging. Using an adenoassociated virus (AAV) to selectively overexpress the PDE4A5 isoform, Havekes and colleagues showed that increasing protein levels of the PDE4A5 isoform specifically in mouse hippocampal excitatory neurons impairs forskolin-induced hippocampal L-LTP and attenuates hippocampus-dependent long-term memory in the Object Location Memory (OLM) and contextual fear conditioning tasks (Havekes et al., 2016a). Interestingly, overexpression of PDE4A5 did not impact short-term memory or anxiety-related behaviors. The latter observation indicates that the PDE4A isoforms affecting memory function and anxiety-related behaviors might be different. Alternatively, it may be that PDE4A5 expression in regions other than the hippocampus (*e.g.*, the amygdala or prefrontal cortex) regulates anxiety-related behaviors. Importantly, viral expression of a truncated version of PDE4A5, which lacks the unique N-terminal domain required to properly localize the enzyme, did not affect long-term memory. Likewise, overexpression of the PDE4A1 isoform, which targets a different subset of signalosomes, leaves memory undisturbed. This finding underscores the notion that it is PDE4A5 and its proper localization that acts as a molecular constraint on hippocampal memory and synaptic plasticity.

4.3.2.2. PDE4B. In contrast to PDE4A, it appears only select pools of PDE4B play a role in hippocampus-dependent memory. Several groups report that mice lacking PDE4B show normal learning in the MWM, standard passive avoidance task, and/or contextual fear conditioning (Siuciak et al., 2008a; Zhang et al., 2008a;Rutten et al., 2011). Surprisingly, PDE4B knockout mice show reduced sensorimotor gating in the prepulse inhibition of acoustic startle (PPI) task relative to wild-type mice (Siuciak et al., 2008a), despite the fact that global inhibition of the PDE4 family using rolipram strongly increases PPI (Kanes et al., 2007; Kelly et al., 2007; Siuciak et al., 2007a). Although PDE4B KO mice exhibit normal tetanus-induced and theta burst-induced long-lasting Schaffer collateral LTP, they show increased basal synaptic transmission and enhanced Schaffer collateral LTD (Rutten et al., 2011). This may explain why PDE4B mice are normal during initial learning but are impaired on reversal learning in the MWM (Rutten et al., 2011).

More recently, groups have adopted a dominant negative approach to specifically interrogate the function of the PDE4B1 isoform. The Bolger lab developed transgenic mice that expressed a PDE4B1-D564A mutant that exhibited reduced catalytic activity (Campbell et al., 2017). Expression of a dominant negative mutation such as this will compete for binding with endogenously expressed PDE4B1, thus reducing PDE4B1 activity within specific signalosomes. PDE4B1-D546A transgenic mice exhibited increased phosphorylation of CREB and ERK in the hippocampus, enhanced basal synaptic transmission, paired-pulse facilitation, and long-lasting Schaffer collateral LTP, but normal memory for contextual and cued fear conditioning (Campbell et al., 2017). In contrast, the Rodefer lab developed a PDE4B1-Y358C mutation, which models schizophrenia-associated mutations that prevent PDE4B from binding to the hub protein *disrupted in schizophrenia 1 (*Millar et al., 2005*)*. PDE4B1-Y358C transgenic mice showed increased CREB phosphorylation along with improved spatial working memory in the Y-maze, object location memory, social recognition memory, as well as learning, reversal learning, and memory on the MWM (McGirr et al., 2016). Surprisingly, however, these mice showed impaired contextual and cued fear conditioning 7 days after training, which authors attributed to increased hippocampal neurogenesis (McGirr et al., 2016). These behavioral phenotypes are associated with enhanced forskolin-stimulated and tetanic-stimulated Schaffer Collateral LTP, but impaired depotentiation of this circuit (McGirr et al., 2016). Together, these data suggest that any one PDE4B-containing macromolecular complex regulates only limited aspects of hippocampus-dependent plasticity and behavior, and that one PDE4B complex might cancel out the effect of another depending on what other signaling molecules are present at the time.

PDE4D. The role PDE4D plays in hippocampus-dependent memory and plasticity may not be as straight forward as that described above for PDE4A. Deletion of PDE4D increases cell proliferation and phosphorylation of CREB in the mouse hippocampus (Li et al., 2011). Conventional PDE4D knockout mice showed enhanced LTP in area CA1 relative to wild-type mice when a subthreshold tetanic stimulation or theta burst protocol was employed, but equivalent LTP when a long-lasting LTP induction protocol was used (Rutten et al., 2008). PDE4D knockout mice also exhibited improved recent long-term memory on both the radial arm maze and the MWM 24 h after training (Li et al., 2011), but weaker recent long-term memory for contextual fear conditioning (Rutten et al., 2008). This contextual fear conditioning phenotype in the global knockout may reflect signaling changes outside of the hippocampus (*e.g.*, amygdala) because selective knockdown of PDE4D in the hippocampus alone improved recent long-term memory for contextual fear conditioning and increased the number of training-induced stubby spines in CA1 (Baumgartel et al., 2018). Thus, these data argue that PDE4D within the hippocampus represents a negative regulator of hippocampal plasticity and memory.

Region-specific manipulations suggest that it is the long forms of PDE4D specifically—both within and outside of the hippocampus—that are a molecular constraint for hippocampus-dependent memories. Selective knock down of PDE4 long-forms (*i.e.*, PDE4D4 and PDE4D5 but not PDE4D1/2 nor PDE4D3) within the dentate gyrus of the hippocampus strengthened recent long-term memory in the radial arm maze, MWM, and object recognition tests (Li et al., 2011) and reveresed Aβ-42-induced memory impairments in the MWM and object recognition tasks (Zhang et al., 2014). Biochemical analyses showed that selective knockdown of PDE4D long forms increased phosphorylation of CREB and cell proliferation in the hippocampus as did the global knockout of PDE4D (Li et al., 2011). Thus, PDE4D4 and PDE4D5 play particularly critical roles as negative regulators of hippocampal neuroplasticity, cell proliferation, and memory formation.

Together, these data suggest that specific PDE4A and PDE4D

isoforms may be particularly interesting therapeutic targets for the treatment of memory dysfunctions. It is important to note, however, that broad spectrum PDE4 inhibitors characterized to date are associated with emetic and other gastrointestinal side effects, most likely due to inhibition of PDE4 within the area postrema (for review, see (Baillie et al., 2019)). From a therapeutic perspective, it would be preferable to only target those splice variants that exhibit disease-related changes in function, and to only target those isoforms in relevant brain regions. Thus, it might be possible to not only avoid emesis and other GI-related side effects, but also triggering other cognitive deficits (e.g., issues with attention or working memory). As discussed elsewhere (Baillie et al., 2019), such brain-region specific targeting of therapeutics may be on the horizon with emerging advances in drug delivery and gene therapy methodologies.

4.3.3. Phosphodiesterase 8

The PDE8 family is also cAMP-specific and comprised of two genes, PDE8A and PDE8B (Beavo, 1995). Where PDE8A expression is largely restricted to white matter in the CNS, PDE8B can be found in gray matter, including that of the dentate gyrus and CA1 region of hippocampus (Kelly et al., 2014). As described by Tsai and colleagues (Tsai et al., 2012), genetic ablation of PDE8B enhances recent long-term memory for contextual fear conditioning and MWM. Importantly, memory for delayed cued fear conditioning remained intact in the PDE8B KO mice, suggesting their contextual fear conditioning memory enhancement reflects altered hippocampal function as opposed to a change in the amygdala. As a result, inhibition of PDE8B might seem to be an interesting therapeutic approach for improving memory function. That said, PDE8B knockout mice also show higher levels of anxiety-related behavior, possibly limiting the potential of PDE8B as a therapeutic target (Tsai et al., 2012).

4.3.4. Phosphodiesterase 10

PDE10 is a dual substrate family encoded by one gene, *i.e.* PDE10A (Beavo, 1995; Menniti et al., 2007). PDE10A is predominantly expressed in striatal medium spiny neurons and is therefore mainly investigated as a therapeutic target for corticostriatal disorders including schizophrenia, Parkinson's disease, and Huntington's disease (Geerts et al., 2017). Nevertheless, some studies have investigated whether its pharmacological inhibition or genetic deletion could be beneficial in the memory domain as it is also expressed at low levels in the adult rodent hippocampus (although not the adult human hippocampus; (Farmer et al., 2020)). PDE10A knockout mice on a DBA1LacJ background showed normal acquisition and memory in the MWM (Siuciak et al., 2006). PDE10A KO mice on either a DBA1LacJ or C57BL/6 N also showed learning deficits in a conditioned avoidance behavior (Siuciak et al., 2006, 2008b). However, this is likely caused by the loss of PDE10A from the striatum, as the striatum rather than the hippocampus is required for acquisition and maintenance of conditioned avoidance (Oleson and Cheer, 2013). Selective deletion of the PDE10A2 isoform, the predominant isoform expressed in brain, did not affect contextual fear conditioning memory but did increase sociability of male mice (Sano et al., 2008). This effect may be related to hippocampal PDE10A2, specifically, because increasing PDE10A expression in the nervous system via knockdown of its cognate microRNA (Mir137) reduced sociability in mice while also impairing LTP, social recognition memory, and MWM learning (Cheng et al., 2018a,b). That said, many other targets both in and outside of the hippocampus are changed in response to Mir137 knock down (*e.g.*, the catalytic subunit of PKA) (Cheng et al., 2018a,b). Together, these studies raise the possibility that PDE10A may play a limited role in hippocampus-dependent memories in rodents; however, hippocampus-specific manipulations of PDE10 signaling will be required to establish this firmly.

4.3.5. Phosphodiesterase 11

The PDE11 family of cyclic nucleotide PDEs is also a dual substrate family hydrolyzing both cAMP and cGMP and is encoded by the PDE11A gene (Beavo, 1995; Kelly, 2017). PDE11A contains four different isoforms (PDE11A1-4) of which PDE11A4 is highly expressed in the ventral hippocampal formation (Kelly, 2015) and low levels are noted in the dorsal hippocampus, spinal cord, and dorsal root ganglion (Kelly, 2018b). Outside of the nervous system, PDE11A expression appears to be sparse (Kelly, 2015). PDE11A4 is the only PDE whose expression in the brain originates solely from the hippocampal formation (Kelly et al., 2014). This highly selective expression profile would provide an ideal candidate for targeting hippocampal memory function, as it would enable selective therapeutic targeting of the brain region of interest while avoiding other brain regions or peripheral organs that might lead to side effects. Deletion of PDE11A alters social interactions as well as the formation of social memories (Hegde et al., 2016a, b; Kelly et al., 2010). Relative to wild-type littermates, PDE11A knockout mice exhibit normal short-term memory for social odor recognition and social transmission of food preference, but showed impaired recent long-term memory 24 h post training. Importantly, PDE11A knockout mice showed normal long-term memory for non-social odor recognition at the 24 h time point. Interestingly, however, PDE11A knockout mice go on to show stronger remote long-term memory for social odor recognition and social transmission of food preference 7 days after training (Pilarzyk et al., 2019). This transient amnesia correlates with changes in the overal activation and functional connectivity of hippocampal/parahippocampal brain regions and frontal cortical regions (Pilarzyk et al., 2019). Importantly, viral restoration of PDE11A4 selectively to ventral CA1 was sufficient to reverse the transient amnesia for social memories that was observed in PDE11A KO mice, again without affecting non-social memories.

The work described above again emphasizes the importance to study subregion-specific modulation of cyclic nucleotide signaling as social memories are strongly associated with area CA1. It also highlights the benefit of targeting specific PDE subtypes, isoforms, or compartments. Indeed, genetic deletion of the PDE11A4 isoform provides the opportunity to distinguish between recent and remote long-term memory consolidation, which has not been shown previously for any other PDE family.

4.4. Genetic manipulation of protein kinase A

As a reminder, PKA is a heteroligomer composed of 2 regulatory subunits and 2 catalytic subunits. The regulatory subunits bind cAMP to activate the enzyme and anchoring proteins to properly localize the enzyme to relevant signalosomes. Studies utilizing genetic manipulations to study the role of PKA in hippocampal plasticity and memory have targeted expression, catalytic activity, and protein-protein interactions.

4.4.1. Regulatory subunits

Genetic manipulations of PKA regulatory subunits suggest a differing role for RIβ and RII subunits in hippocampal plasticity and memory. Although RIβ knockout mice showed normal Schaffer collateral LTP relative to wild-type mice, they failed to maintain LTD and demonstrated attenuated depotentiation of this pathway (Brandon et al., 1995). RIβ knockout mice also failed to develop performant path LTD (Brandon et al., 1995), and both the induction and maintenance of mossy fiber LTP are profoundly impaired in RIβ knockout mic (Huang et al., 1995). The fact that RIβ knockout mice exhibited normal Schaffer collateral LTP is consistent with the fact that RII subunits are thought to be the primary means by which PKA participates in this form of plasticity (Wong and Scott, 2004). Despite these strong effects on hippocampal plasticity, RIβ knockout mice showed normal hippocampal learning and memory in contextual fear conditioning, the MWM, and the Barnes maze (Huang et al., 1995). Although LTP/LTD are often conceptualized as cellular models of learning and memory, this is not the only report in which genetic manipulation of cyclic nucleotide

signaling has contrary effects on plasticity and memory (*e.g.*, overexpression of either a normal or constitutively active Gαs strengthens LTP yet impairs hippocampus-dependent memory (Bourtchouladze et al., 2006; Kelly et al., 2007, 2009).

The physiological role of the RIα subunit was explored using a dominant negative approach. R(AB) transgenic mice (Abel et al., 1997; Isiegas et al., 2006) express a mutated form of the regulatory RIα subunit that maintains its ability to bind catalytic subunits but is unresponsive to cAMP. Expression of the R(AB) transgene was restricted to excitatory forebrain neurons, including those in the hippocampus, by driving expression via a CaMKII promotor. Transgenic expression of this inhibitory isoform reduced hippocampal PKA activity (Abel et al., 1997; Isiegas et al., 2006) and impaired long-lasting—but not early—Schaffer collateral LTP induced by 4x100 Hz stimulation (Abel et al., 1997). Consistent with this plasticity profile, R(AB) transgenic mice showed normal spatial learning but impaired recent long-term memory on the MWM, as well as normal short-term memory but impaired recent long-term memory and facilitated extinction of contextual fear conditioning (Abel et al., 1997; Isiegas et al., 2006). The fact that recent-long term memory for cued fear conditioning remains intact in R(AB) transgenic mice suggests the fear conditioning deficit noted above is related to hippocampal pathophysiology as opposed to amygdala dysfunction (Abel et al., 1997). Together, these data argue that RIα plays a critical role in regulating the consolidation and maintenance of hippocampus-dependent long-term memories and LTP.

Loss of the RIIβ subunit produces different phenotypes than those noted above in RIβ knockout mice. The RIIβ subunit links PKA to NMDA receptors at synaptic sites (Yang et al., 2009). Consistent with this fact, RIIβ knockout mice show changes in NMDA receptor-dependent forms of plasticity. From postnatal day 10–14, RIIβ knockout mice exhibit deficits in NMDA receptor-dependent Schaffer collateral LTP, but normal NMDA receptor-dependent LTD (Yang et al., 2009). In contrast, from P21 to P28, RIIβ knockout mice show normal LTP but deficient LTD. These findings indicate that distinct PKA isoforms subserve differing forms of synaptic plasticity and the roles for these distinct PKA isoforms may evolve across the lifespan.

Anchoring, as opposed to expression, of regulatory subunits has also been genetically manipulated to specifically interrogate the need to properly anchor PKA within specific subcellular compartments. Ht31 transgenic mice express a peptide that includes the PKA binding domain of AKAP-Lbc (Nie et al., 2007; Park et al., 2014). This peptide acts as a negative sink in that binding of Ht31 to PKA prevents PKA from binding other AKAPs. This displacement of PKA from relevant signalosomes reduces phosphorylation of protein phosphatase I and the AMPA receptor subunit GluA1 (Kim et al., 2011; Nie et al., 2007). Within the Schaffer collateral pathway, expression of Ht31 postsynaptically (i.e., only in CA1) or both presynaptically and postsynaptically (i.e., in both CA3 and CA1) was not sufficient to affect basal synaptic transmission, paired pulse facilitation, early LTP induced by tetanic stimulation, nor LTD. In contrast, transgenic expression of Ht31 postsynaptically was sufficient to impair long-lasting LTP induced by tetanic stimulation, while transgenic expression of Ht31 both presynaptically and postsynaptically was required to impair long-lasting LTP induced by theta burst stimulation, long-lasting LTP induced by forskolin, as well as synaptic tagging (Nie et al., 2007; Park et al., 2014). Similarly, disruption of PKA anchoring in CA1 alone was not sufficient to impair recent long-term memory in the MWM nor contextual fear conditioning; however, disruption of PKA anchoring in both CA3 and CA1 was sufficient to drive long-term memory deficits in these assays (Nie et al., 2007; Park et al., 2014). PKA binding to gravin-α (a.k.a. AKAP12) may be particularly important for hippocampal function. Conventional gravin-α knockout mice show impairments in hippocampus-dependent forms of learning (*e.g.* MWM, contextual fear conditioning, OLM) as well as deficits in L-LTP (Havekes et al., 2012). That said, these mice also show attenuated performance in the novel object recognition and tone-cued fear conditioning task, suggesting deficits on "hippocampus-dependent" tasks could be driven by altered signaling in the perirhinal cortex and/or amygdala as opposed to the hippocampus. Biochemical analyses indicated that gravin-mediated PKA signaling plays an essential role in the crosstalk between glutamatergic and noradrenergic signaling pathways, consistent with the types of memory and LTP deficits described above (Havekes et al., 2012). In contrast, knockin mice harboring a mutation that prevented PKA from specifically binding AKAP5 (also known as AKAP79/150) showed impaired Schaffer collateral LTP and LTD; however, spatial learning and memory in the MWM remained intact as did memory for novel object recognition (Sanderson et al., 2016; Weisenhaus et al., 2010). Altogether, these data argue that the proper localization of PKA to specific AKAP complexes, particularly those within CA3 presynaptic compartments, is important for hippocampus-dependent memories and long-lasting forms of LTP.

4.4.2. Catalytic subunits

One study reported effects of genetically deleting a PKA catalytic subunit, specifically the Cβ1 subunit (Qi et al., 1996). Deletion of Cβ1 was not sufficient to change basal or cAMP-stimulated PKA activity, possibly due to the fact that Cβ1 is responsible for only ~10 % of total PKA activity (Qi et al., 1996). This genetic manipulation was, however, sufficient to alter hippocampal plasticity. Although paired pulse facilitation and early Schaffer collateral LTP remained intact, late LTP, LTD, and depotentiation of this pathway were impaired in Cβ1 knockout mice relative to wild-type mice (Qi et al., 1996).

Taken together, these data suggest PKA plays a critical role in the consolidation of hippocampus-dependent memory and long-lasting forms of plasticity. They also underscore the importance of taking into account regional differences in the expression and manipulation of individual PKA subunits and binding partners, as there are clearly diverging phenotypes depending on the subunit and hippocampal subfield targeted/interrogated.

4.5. Genetic manipulation of exchange protein directly activated by cAMP (EPAC)

As mentioned previously, Epac represents a family of cAMP-binding effector proteins that regulate several intracellular pathways and signaling processes (Cheng et al., 2008; de Rooij et al., 1998; Kawasaki et al., 1998; Woolfrey et al., 2009), including neural stem/progenitor cell proliferation in the hippocampus (Zhou et al., 2018). Epacs exchange guanine nucleotides on small G proteins, such as Rap. In so doing, they can act as a molecular switch from cAMP to downstream cGMP signaling pathwys that are critical for neurotransmitter release (Gekel and Neher, 2008; Zhong and Zucker, 2005), integrin cell adhesion (Enserink et al., 2004; Rangarajan et al., 2003), and gene expression (Sands et al., 2006, 2012). Early electrophysiological studies suggested that deletion of either Epac1 or Epac2 was not sufficient to affect LTP; however, deletion of both isoforms reduced glutamate release from presynaptic terminals in CA1 and caused a profound deficit in long-lasting LTP (Yang et al., 2012). Epac1/2 double knockout mice also exhibited more severe deficits in granule cell LTP relative to single knockout mice; however, no changes in LTD were noted in this study (Yang et al., 2012). The effect of Epac deletion on granule cell LTP appears to be driven by reduced glutamate release that is caused by an increased open probably of inwardly rectifying potassium channels in the dentate gyrus (Zhao et al., 2013). In a later study, mossy fiber LTP and cAMP-mediated potentiation of transmitter release were found to be reduced in Epac2 knockout mice relative to wild-type mice, due to smaller active zones and fewer synaptic vesicles in the readily releasable pool (Fernandes et al., 2015). In this later study, Epac2 knockout mice also demonstrated a slightly weaker induction of early Schaffer collateral LTP and stronger LTD (Lee et al., 2015). These electrophysiological changes do not appear to be related to gross morphological changes in CA1 as ultrastructure in the single and double

knockout mice appear normal (Yang et al., 2012).

In terms of behavior, early studies suggested that pharmacological activation of Epac immediately after training was sufficient to strengthen basal short-term and recent long-term memory for contextual fear conditioning (Kelly et al., 2009) and partially reverse long-term memory deficits in contextual fear memory caused by depletion of norepinephrine (Ouyang et al., 2008). A later study, however, suggested that pharmacological activation of Epac was only able to improve retrieval of a contextual fear conditioning memory, not its consolidation (Ostroveanu et al., 2010). The ability of the Epac agonist to improve memory retrieval was also observed in a standard passive avoidance paradigm (Ostroveanu et al., 2010). These pharmacological effects are likely mediated via Epac2 specifically because knockdown of this isoform in the hippocampus using an siRNA impaired retrieval of a recent long-term memory 72 h after fear conditioniong and blocked the ability of the Epac agonist to improve retrieval at this time point (Ostroveanu et al., 2010). Interestingly, no effect of intrahippocampally infusing the Epac agonist nor Epac2 siRNA was observed when the fear memory was retrieved 14 days after training (Ostroveanu et al., 2010), a time point at which fear conditioning memories begin to rely more on the cortex and less on the hippocampus (Frankland and Bontempi, 2005). Epac2 global knockout mice also showed reduced recent long-term memory for contextual and cued fear conditioning; however, Epac1 knockout mice show no change in recent long-term memory for contextual fear conditioning yet enhanced recent long-term memory for cued fear conditioning (Zhou et al., 2016). A particularly strong role for Epac in fear memories may be related to the fact that stress upregulates expression of Epac1 and Epac2 in the hippocampus and deletion of Epac2 heightens stress-induced serum corticosterone levels, at least in females (Aesoy et al., 2018), or the fact that foot shocks are felt more strongly by Epac2 knockout mice (Lee et al., 2015).

Studies of other types of hippocampus-dependent memories suggest function of Epac1 may compensate for the loss of Epac2 (and vice versa) in some instances. Epac2 knockout mice exhibit normal spatial learning and recent long-term memory in the MWM, normal spatial working memory in the Y-maze, and normal object location memory (Srivastava et al., 2012)(Yang et al., 2012; Lee et al., 2015; Zhou et al., 2016). Epac1 knockout mice also show normal spatial learning and memory in the MWM (Yang et al., 2012). Deletion of both Epac1 and Epac2, however, severely impairs spatial learning and recent long-term memory in the MWM (Yang et al., 2012). Interestingly, the effect of Epac1/2 deletion was blocked by knockdown of the microRNA miR-124 (Yang et al., 2012). Together, these studies suggest the Epacs play a critical role in regulating hippocampal plasticity and memory, but it will be important for future studies to take a more targeted approach in manipulating these isoforms in a region-specific manner.

4.6. Genetic manipulation of protein kinase G

Both global knockouts and hippocampus-targeted knockout mice have been used to probe PKG function in the context of hippocampal function. Early Schaffer-collateral LTP is unaffected by global deletion of PKGI, PKGII, or both isoforms (Kleppisch et al., 1999). That said, deletion of these enzymes led to severe gastrointestinal and cardiovascular defects and a reduced lifespan (Kleppisch et al., 1999), the influence of which may have obscured an accurate assessment of hippocampal plasticity (Schlossman et al., 2005). As such, Kleppisch and colleagues generated PKG-I conditional knockout mice (Kleppisch et al., 2004). By crossing these conditional knockouts with a NEX-Cre driver line, deletion of PKG-I was restricted to the CA fields of the hippocampus, thus avoiding effects on gastrointestinal and cardiovascular function as well as life expectancy (Kleppisch et al., 2003). Early Schaffer collateral LTP was normal in both adolescent and young adult PKGI cKO mice (Kleppisch et al., 2003), supporting findings described above in the global knockout. In contrast, long-lasting LTP induced by repetitive theta-burst stimulation was impaired in the adult PKGI cKOs relative to normal mice (Kleppisch et al., 2003). Specifically, PKGI cKOs were able to achieve equivalent potentiation following the initial theta burst stimulation, but failed to demonstrate an augmentation of that potentiation with successive bouts of stimulation. Interestingly, this heightened potentiation that comes with successive theta-burst stimulations is protein-synthesis dependent in adults and does not appear to occur in juvenile mice (Kleppisch et al., 2003). Given that juveniles lack this protein-synthesis dependent form of LTP, it is no surprise then that adolescent PKG-1 cKO mice did not differ from normal adolescent mice (Kleppisch et al., 2003). Despite these effects on plasticity, the adult PKGI cKOs showed normal acquisition, memory and reversal learning in a discriminatory water maze task and normal memory in contextual and cued fear conditioning.

Although PKGII is much less abundantly expressed in the hippocampal formation than PKGI, it may play a more significant role in hippocampal memory. PKGII conventional knockout mice show significantly deficient spatial learning in the MWM and somewhat impaired short-term memory in the MWM (normal time in the target quadrant but reduced platform crossings; Wincott et al., 2013). It is unlikely that the increased latency to find the platform during MWM training is related to locomotor issues, as PKGII KO mice show normal locomotor activity in an open field and actually show stronger motor coordination on the rotarod (Wincott et al., 2013). Interestingly, these learning and memory deficits are associated with an upregulation of the AMPA receptor subunit GluA1 in PKGII KO mice relative to wild-type mice (Wincott et al., 2013). It remains to be determined, however, whether this upregulation of GluA1 reflects a signaling deficit or an attempt of the hippocampus to compensate for lost function.

Clearly more studies are needed to better understand the functional role of PKG signaling in the hippocampus. More targeted genetic manipulations of these enzymes within the hippocampus, along with a more thorough characterization of plasticity types (i.e., mossy fiber LTP, performant path LTP, LTD, etc.) and hippocampus-dependent memory types (*e.g.*, social memories that are more dependent on the ventral hippocampus), will improve our understanding of exactly where PKG may influence hippocampal function. Initial studies suggest age will be an important factor when probing the function of these enzymes, which may not be surprising given the number of age-related changes that occur within the cyclic nucleotide signaling cascades (Kelly, 2018a).

4.7. Chemogenetic manipulation of cyclic nucleotide signaling

Chemogenetic approaches employ naturally occurring or engineered molecules that retain GPCR-like structure and function, but are only activated by compounds/molecules that do not normally exist in mammalian systems. Expression of these recombinant molecules in the brain is often driven by a cell-type specific promoter (*e.g.*, CamKII to target pyramidal neurons) using either transgenic or viral technologies. To modify signaling within one specific brain region, one can either 1) express the transgene everywhere and then stereotaxically deliver the activating compound or 2) virally deliver the transgene to a restricted brain region and then deliver the activating compound either locally or, in theory, systemically (since the compound should only act on the recombinant receptor itself). Although spatial resolution is relatively easy to achieve with chemogenetic approaches, the temporal precision is limited by the pharmacokinetics of the compounds used to activate them (Gomez et al., 2017; Guettier et al., 2009). As discussed in the introduction, cAMP signaling is initiated following the activation of Gs-coupled GPCRs and inhibited following the activation of Gi-coupled GPCRs (Wang and Storm, 2003). Chemogenetic molecules are based on these GPCR cascades but do not recognize any endogenous molecules in mammalian systems either because they originate from a non-mammalian system or because they have been genetically engineered.

One of the first chemogenetic approaches was developed by the Abel lab (Isiegas et al., 2008), and involved conditional expression of

the *Aplysia-specific* octopamine Gs-coupled receptor. Expression of the receptor was restricted to forebrain excitatory neurons of mice using the CaMKII promoter. The octopamine receptor is activated by its natural ligand octopamine, which does not naturally exist in mammalian systems but can rapidly and transiently increase cAMP in mammalian cells when the octopamine receptor is recombinantly expressed (Isiegas et al., 2008). As expected, administration of octopamine to the transgenic mice led to a rapid elevation in hippocampal cAMP levels. Although basal synaptic transmission remained unaffected, octopamine administration to transgenic mice made an early LTP induction protocol trigger long-lasting LTP within the Schaffer collateral pathway (Isiegas et al., 2008). Octopamine administration 30 min before training, 3 h—but not immediately—after training, or 30 min prior to retrieval all enhanced recent long-term memory (24 h after training) for contextual fear conditioning in transgenic mice. Systemic injection 30 min before training also improved short-term memory (1 h after training) for contextual fear conditioning and recent long-term memory (24 h after training) for object recognition memory. Together, these data suggest that elevating cAMP during acquisition, later consolidation, or retrieval is sufficient to strengthen hippocampus-dependent memory. Importantly, the finding that cAMP signaling is particularly important for late-stage consolidation and not that immediately following training was later confirmed using pharmacological manipulation of cAMP (*e.g.*, Bollen et al., 2014).

Later studies using chemogenetic approaches employed 'Receptors Activated Soley by a Synthetic Ligand' (RASSLs) or 'Designer Receptors Exclusively Activated by Designer Drugs' (DREADDs). Clozapine N-oxide (CNO), a pharmacologically inert metabolite of the antipsychotic drug clozapine, has been the most commonly used designer drug (Armbruster et al., 2007; Roth, 2016). CNO has its limitations, however, as a fraction of systemically-administered CNO is metabolized back to clozapine (Jann et al., 1994; MacLaren et al., 2016), which more readily crosses the blood brain barrier (Cremers et al., 2012; Hellman et al., 2016), more potently binds DREADDs (Armbruster et al., 2007), and has its own central effects (Mahler and Aston-Jones, 2018). Thus, more recent efforts have focused on developing alternative 'designer drugs' for existing and newly engineered designer receptors (Roth, 2016).

The G_s-coupled DREADDs (GsD and rM3D) increase cAMP levels when the activated Gα subunit stimulates adenylate cyclase, while the G_i-coupled DREADDs (hM4Di and KORD) decrease cAMP levels when the activated Gα subunit inhibits adenylate cyclase (Roth, 2016). Unfortunately, activation of a G_i-coupled DREADD can also activate GIRKs, alter β-arrestin signaling and impact Ca^{2+} (Armbruster et al., 2007; Rogan and Roth, 2011; Saloman et al., 2016). As such, it is not possible to discern whether effects of G_i-coupled DREADDs on hippocampal plasticity and memory (e.g., Alexander et al., 2018; Jones et al., 2018; Lopez et al., 2016; Nam et al., 2019; Ortiz et al., 2019; Park et al., 2016; Tuscher et al., 2018; Varela et al., 2016; Zhu et al., 2014) are mediated by reductions in cAMP signaling or effects on other downstream signaling pathways. Although several reports have used G_s-coupled DREADDs to study the role of the striatum or other brain regions in a variety of behaviors (*e.g.*, (Oliver et al., 2019; Pleil et al., 2015; Ferguson et al., 2013; Farrell et al., 2013; Brancaccio et al., 2013), only one study has reported effects on a hippocampus-dependent memory. In this one study, activating rM3D DREADDs selectively in the hypothalamic hypocretin/orexin system, which is known to project to the hippocampus, improved short-term spatial memory but not novel object memory (Aitta-Aho et al., 2016).

Together, these findings provide proof of principal for utilizing chemogenetic approaches to study the role of cyclic nucleotide signaling in the context of hippocampal function. That said, these powerful tools have clearly been underutilized in this realm. It will be of interest to future studies to use these tools to study the role cAMP plays within specific cell types within the hippocampus by using cell-type specific promoters to drive their expression. It will also be highly interesting to couple this technology with conditional expression systems that enable the selective manipulation of cAMP signaling within one specific hippocampal circuit at a time (*e.g.* ventral CA1 → to nucleus accumbens). Although all DREADDs to date are based on GPCRs, it would also be interesting to explore the possibility of engineering particulate guanylate cyclase receptors into cGMP-regulating DREADDs to expand the neuroscience toolbox even further. Even though chemogenetic studies are limited, the results to date support the notion that acute increases in cAMP levels within hippocampal neurons, or neurons that project to the hippocampus, facilitate hippocampal neuroplasticity and memory.

4.8. Modulation of cyclic nucleotide signaling through optogenetics

Despite the fact that transgenic, viral and chemogenetic approaches allow us to conditionally modulate cyclic nucleotide signaling in a cell type-specific fashion, there are temporal limitations to these approaches with a resolution ranging from minutes to hours. Optogenetics tools do not suffer this limitation. In the case of classical optogenetics, neurons are genetically modified to express one of three classes of microbial light-sensitive proteins called 'opsins', which, when activated by light, cause neuronal excitation or inhibition. The first class, 'bacteriorhodopsins', pump protons out of the cell causing hyperpolarization when inserted into a neuron and subsequently lead to neuronal inhibition. The second class, 'halorhodopsins', cause hyperpolarization of neurons and neuronal inhibition by pumping negatively charged chloride ions into the cell. Thirdly, 'channelrhodopsins' can either excite or inhibit neural systems when inserted into a neuron by allowing positively charged ions to flow into the cell or by chloride conduction, respectively (Boyden et al., 2005; Deisseroth, 2015). Next to these classical membrane-spanning actuators, the optogenetic toolbox has been expanded with soluble light-activated enzymes, photocontrol of protein-protein interactions, and cryptochromes that mediate light-induced protein oligomerization (Rost et al., 2017). The group of soluble light-activated enzymes includes photoactivated cyclases that bind flavin adenine dinucleotide (FAD) and engineered light-activated PDEs that use biliverdin as a chromophore, both permitting optogenetic control of cyclic nucleotide signaling (Rost et al., 2017).

Several adenylate cyclase optogenetic molecules have also been developed. The first 'photoactivated adenylate cyclase' (PAC), named 'euPAC', was identified in *Euglena gracilis* in which it serves a role in photoavoidance. This adenylate cyclase has a heterotetrameric structure consisting of two PACα and PACβ subunits that are activated by blue light and four catalytic domains homologous to group III adenylate cyclases (Iseki et al., 2002). The functional expression of PACα and PACβ was verified in different systems including *Xenopus laevis* oocytes, HEK293 cells, *Aplysia* and *Drosophila melanogaster* (Nagahama et al., 2007; Schroder-Lang et al., 2007). Unfortunately, the large size and high basal activity in the absence of light prevented the wide application of euPAC in other organisms. Another PAC, named 'BlaC', was engineered by the Gomelsky lab. The construct contained the *blaC* gene encoding a group III adenylate cyclase isolated from *Beggiatoa sp.* and one BLUF domain (sensors of blue-light using FAD), significantly decreasing size (Ryu et al., 2010). At approximately the same time, the lab of Hegemann validated the efficacy of the same protein, which they named 'bPAC' (Stierl et al., 2010). In *Escherichia coli* and *Xenopus* oocytes, bPAC showed low cyclase activity in the absence of light that is increased by 300-fold in the light. More importantly, the applicability of bPAC was proven in rat cortical neurons (Stierl et al., 2010), *Drosophila* nervous system (Efetova et al., 2012; Stierl et al., 2010) as well as zebrafish (Brancaccio et al., 2013; De Marco et al., 2016; Gutierrez-Triana et al., 2015). More recently a blue light-regulated adenylate cyclase was identified in *Microcoleus chthonoplastes*, therefore termed 'mPAC'. This enzyme contains a photoreceptive LOV domain and exhibits higher constitutive activity in comparison to euPAC and BlaC/bPAC, but also higher activity after blue light irradiation (Chen et al., 2014; Raffelberg et al., 2013). Although exhibiting a promising

dynamic range, extensive use of these PACs was restricted due to disadvantages including low tissue penetration and photooxidative damage by the blue light (Hockberger et al., 1999).

To overcome these limitations, the Gomelsky lab engineered the first synthetic PACs activated in the near-infrared window (NIRW) (Ryu et al., 2014). Their 'Ilac' construct contains a photosensory module from the *Rhodobacter sphaeroides* bacteriophytochrome DGC, BphG1 and a type III adenylate cyclase domain from the Nostoc sp. CyaB1 protein. The effectiveness of Ilac was validated in *Caenorhabditis elegans* in which exposure of red light to cholinergic neurons resulted in elevation of cAMP/PKA signaling and subsequent altered locomotor behavior (Ryu et al., 2014). Recently, the same group engineered a successor, designated 'IlaM5', which has several advantages over previous NIRW-adenylate cyclases. For example, IlaM5 has significantly higher activity at 37 °C, is better expressed in mammalian cells, and can mediate NIRW-induced gene expression through activation of the cAMP pathway in mammalian cells (Fomicheva et al., 2019). The IlaM5 gene expressed from an AAV vector was delivered into the ventral basal thalamus region of the mouse brain, resulting in the light-controlled suppression of the cAMP-dependent spindle oscillations of the sleeping brain (Fomicheva et al., 2019). Reversible spindle oscillation suppression was observed in sleeping mice exposed to NIRW light from an external light source without the need for fiber optic cables (Fomicheva et al., 2019). This ultimately confirms the robustness of principles of homodimeric bacteriophytochrome engineering, supports the notion that NIRW-adenylate cyclases are finally suitable for mammalian optogenetic applications, and that controlling brain activity via NIRW-adenylate cyclases using transcranial irradiation is feasible. Moreover, the generation of NIRW-activated adenylate cyclases provides the opportunity to combine optogenetics with imaging techniques for detecting or manipulating cyclic nucleotide signaling. Together, it results in extremely high spatial and temporal resolution without the need for fiber optic cables or connectors attached to the head of the animal that could interfere with normal behavior.

Photoactivated guanylate cycleases have also been developed. The first photoactivated guanylate cyclases were engineered by inducing multiple mutations in the *Beggiatoa* BlaC. The resulting triple mutant, designated 'BlgC', was shown to exhibit guanylate cyclase activity *in vitro* and significant increases in cGMP production *in vivo* after irradiation with blue light (Ryu et al., 2010). The first natural light-activated guanylate cyclase was identified in the fungus *Blastocladiella emersonii* by the group of Gomes and named 'BeGC1' (Avelar et al., 2015; Scheib et al., 2015). It consists of rhodopsin fused to the catalytic domain of guanylate cyclase and is activated by green light. The efficacy of the enzyme was confirmed in *in vitro* and *in vivo* assays including HEK293 T cells, *Xenopus* oocytes, muscle cells of *Caenorhabditis elegans*, mammalian ovary cells and cortical neurons (Gao et al., 2015; Scheib et al., 2015). The Gomelsky lab also engineered a NIRW-activated construct for the production of cGMP (Ryu and Gomelsky, 2014). The chimeric construct was comprised of a bacteriophytochrome c-di-GMP synthase (diguanylate cyclase, DGC) originating from the *Rhodobacter sphaeroides* BphG1 protein and a constitutive c-di-GMP-specific PDE, YhjH, from *E. coli*. DGC is not endogenously expressed in higher eukaryotes and has potential to regulate cGMP signaling in mammals (Ryu and Gomelsky, 2014).

In addition to optogenetic manipulation of cyclic nucleotide production by development of light-sensitive cyclases, similar attempts have been made to optogenetically target the degradation of cyclic nucleotides by the engineering of light-activated PDEs (LAPD). The first LAPD was comprised of the photosensor module of *Deinococcus radiodurans* bacterial phytochrome and the effector module of the human PDE2A (Gasser et al., 2014). Since PDE2A is a dual-substrate PDE, the photoactivated construct also has dual substrate specificity, and illumination with red light enhances the hydrolysis of both cGMP and cAMP by 4–6 fold. Moreover, exposure of LAPD to far-red light decreases its activity. LAPDs have shown to efficiently increase cyclic nucleotide hydrolysis in eukaryotic cell cultures and zebrafish embryos (Gasser et al., 2014). Two other groups isolated a similar dual substrate enzyme with PDE activity from the choanoflagellate *Salpingoeca rosetta* (Lamarche et al., 2017; Yoshida et al., 2017). The 'Rh-PDE' or 'RhoPDE', as it was named by the different groups, is a fusion of rhodopsin type I with PDE. Unfortunately, the enzyme displays only a minimum amount of light-dependent PDE activity. It can again hydrolyze both cyclic nucleotides, but with higher selectivity for cGMP over cAMP (Lamarche et al., 2017; Tian et al., 2018; Yoshida et al., 2017). Crystallography of the isolated PDE domain of the enzyme showed high resemblance in terms of sequence and structure to the human PDE9 (Lamarche et al., 2017).

Modulation of cyclic nucleotide signaling through optogenetics is currently the optimal technique in the genetic domain to achieve high spatial and temporal resolution. The recent generation of NIRW-activated adenylate cyclases removes the need for fiber optic cables and connectors, eliminating their interference with normal mammalian behavior. This also provides the opportunity to combine optogenetics with imaging techniques for detecting or manipulating cyclic nucleotide signaling. Together, it results in extremely high spatial and temporal resolution making the NIRW-activated cyclases very suitable to study the spatial and temporal dynamics of cyclic nucleotide signaling *in vivo* during neuroplasticity and memory formation. Such spatial and temporal control may also lead to novel therapeutic inroads given that optogenetic-based approaches are being tested in the clinic (Ye and Fussenegger, 2018). For example, being able to activate or inhibit a given PDE using a temporally and spatially restricted light emission would enable a brain-region specific treatment of cyclic nucleotide dysfunction, which is necessary when attempting to treat a disease where cyclic nucleotide signaling is upregulated in one tissue yet downregulated in others (*e.g.*, aging; c.f., (Kelly, 2018a)). Spatially restricting the PDE modulation would also avoid side-effects associated with modifying PDE activity within a specific tissue (*e.g.*, the gastrointestinal side effects caused by PDE4 inhibition in the area postrema).

5. Genetic manipulation of cyclic nucleotide signaling during suboptimal memory formation caused by sleep deprivation

Previous work has shown that sleep deprivation impairs cAMP signaling in the hippocampus leading to deficits in consolidation of contextual fear conditioning memories (Graves et al., 2003; Vecsey et al., 2009). First evidence for the involvement of cAMP in the negative effect of sleep deprivation on memory function came from electrophysiological studies using LTP (Vecsey et al., 2009). Sleep deprivation specifically impaired forms of LTP that depend on the cAMP/PKA pathway, like spaced 4-train LTP and theta burst-induced LTP (Vecsey et al., 2009). When an AAV using the CaMKIIα promoter was used to express the G_s-coupled octopamine receptor selectively in hippocampal excitatory neurons, it was possible to produce transient increases in cAMP levels via activation of the recombinant octopamine receptors. Doing so during the course of sleep deprivation prevented the memory consolidation deficits. These findings demonstrate that attenuated cAMP signaling in hippocampal excitatory neurons is a critical component underlying the memory deficits in hippocampus-dependent learning tasks associated with sleep deprivation.

In two follow-up studies, Havekes and colleagues showed the above sleep deprivation-induced deficits in LTP and memory were associated with structural losses of dendritic spines in area CA1 (Havekes et al., 2016b) and dentate gyrus (Raven et al., 2018) of dorsal hippocampus. Sleep deprivation was found to increase activity of PDE4A5 thereby upregulating activity of the actin-binding protein cofilin via disinhibition of the cAMP-PKA-LIMK pathway (Havekes et al., 2016b). Viral expression of a dominant-negative, catalytically-inactive form of PDE4A5 (referred to as $PDE4A5^{catnull}$) in hippocampal neurons restored cofilin signaling and prevented the behavioral impairments associated with sleep loss. Importantly, the therapeutic effects of the $PDE4A5^{catnull}$

construct required its N-terminal domain, which is responsible for its proper localization within PDE4A5-specific signalosomes. The latter finding again highlights an essential role for the N-terminal domain in targeting PDEs to specific cAMP-containing complexes critical for memory and synaptic plasticity and emphasizes how region- and cell type-specific manipulations of a specific PDE isoform can map out the complete molecular machinery mediating the negative effect of sleep deprivation on hippocampal plasticity and memory function.

6. Discussion & future perspectives

In the current review, we provided a detailed overview of studies using genetic manipulation of cyclic nucleotide signaling to better comprehend their function during hippocampal plasticity and memory formation. The use of genetic approaches has revolutionized our understanding of the molecular mechanisms underlying memory storage. Initially, these genetic approaches used conventional knockout strategies in which genes were inactivated in all tissues throughout the life of the organism. Although studies using these classical knockout strategies have greatly advanced our knowledge of the function of specific genes related to cyclic nucleotide signaling, their use in behavioral and electrophysiological experiments is complicated due to interpretational issues related to developmental alterations, compensation by other biochemical pathways, and lethality.

As a result, new transgenic and conditional methods were developed, each, in their own way, trying to increase spatial resolution. These novel methods have been extensively used over the years in all domains of neuroscience and include the use of the CaMKII promoter to drive gene expression selectively in postnatal neurons in the forebrain (Abel et al., 1997; Mayford et al., 1995), the Cre/LoxP system to selectively delete genes in subsets of neurons (Tsien et al., 1996a, b), and the conditional tetracycline transactivator system (tTA) (Mansuy et al., 1998; Mayford et al., 1996) to turn gene expression on or off. Despite the fact that these systems successfully increased the spatial resolution with which genes can be manipulated compared to conventional gene knockouts, they are still characterized by a relatively poor temporal resolution (Mansuy et al., 1998). Further, using Cre recombinase, genes are irreversibly deleted over a time course of days to weeks even when conditional forms of Cre recombinase are used (Feil et al., 1996; Ratnacaram et al., 2008).

Cyclic nucleotides as well as their effector molecules are activated within a time course of minutes to hours during memory storage (Abel and Lattal, 2001). For instance, both cGMP and cAMP have their specific temporal windows during which they mediate early and late consolidation, respectively (Bollen et al., 2014). This suggests that distinct biochemical processes underlie each of the different memory processes (Abel and Lattal, 2001). Genetic tools have been developed that enable the rapid, reversible regulation of neuronal excitability using optogenetic techniques based on the microbial opsins, channelrhodopsin-2 and halorhodopsin (Zhang et al., 2007). Although these early optogenetic tools provided high temporal resolution, they do not target cyclic nucleotide signaling pathways, but rather alter neuronal excitability. Thus, the development of genetic systems to manipulate intracellular signaling pathways, while maintaining high temporal and spatial resolution, remained. Since the classical membrane-spanning actuators, the optogenetic toolbox has been expanded with soluble light-activated enzymes, photocontrol of protein-protein interactions, and cryptochromes that mediate light-induced protein oligomerization (Rost et al., 2017). The group of soluble light-activated enzymes includes NIRW-photoactivated cyclases that bind flavin adenine dinucleotide (FAD) and engineered light-activated PDEs that use biliverdin as a chromophore, both permitting optogenetic control of cyclic nucleotide signaling. This way, optogenetic modulation of cyclic nucleotide signaling pathways can be achieved with high spatial and temporal resolution, and as previously mentioned, without the need for and interference of fiber optic cables.

Currently, we have arrived at the point in time where we, through the use of genetic models, can obtain regional specificity and isoform/subtype selectivity, linking cyclic nucleotide function to specific memory types and processes. As such, these novel genetic approaches provide excellent means to study the neurobiology of learning and memory, and map the function of cyclic nucleotide signaling pathways with great spatial and temporal resolution. Nevertheless, from a clinical perspective, it is interesting to note how expression levels of the different cyclic nucleotide and their effector molecules change during aging, suboptimal memory formation, and pathological conditions (Kelly, 2018a). To this end, the novel gene CRISPR-Cas9 gene editing technique, seems particularly suited. Using this technique, existing genes can be removed and/or new ones can be added (Cong et al., 2013; Hsu et al., 2014). If we can establish which particular splice variants show increased or decreased expression in the human brain during the course of a disease, CRISPR-Cas9 can be used to overexpress or delete this specific splice variant in a region-specific manner in order to model a particular type of pathology or to gain insight into the contribution of the gene and its product during physiological conditions. In a similar fashion, CRISPR-Cas9 can be used to validate the therapeutic potential of specific target genes minimizing off-target effects. This way, CRISPR-Cas9 gene editing provides a potential next step in the development of genetic approaches to modulate hippocampal cyclic nucleotide signaling cascades (Soto-Velasquez et al., 2018). In conclusion, using optical biosensors along with a variety of genetic manipulations, including chemogenetics, optogenetics, and CRISPR/Cas9 gene editing, we have the means to study the function of cyclic nucleotides and their effectors during both physiological and pathological neuroplasticity and memory formation without spatiotemporal limitations (Humeau and Choquet, 2019).

Declaration of Competing Interest

The authors declare no conflict of interest.

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None.

Appendix A. The Peer Review Overview

The Peer Review Overview associated with this article can be found in the online version, at doi:https://doi.org/10.1016/j.pneurobio.2020.101799.

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